September 1, 1980 volume 138, number 1

merican

23,12

CUK-HO1388-16-PO24280

# Journal Of OBSTETRICS AND GYNECOLOGY

Copyright © 1980 by The C. V. Mosby Company

Editor in Chief
JOHN I. BREWER

Editors

FREDERICK P. ZUSPAN · E. J. QUILLIGAN

Associate Editor
ALBERT B. GERBIE

Emeritus Editors
HOWARD C. TAYLOR, JR. · ALLAN C. BARNES

#### Official Publication

AMERICAN GYNECOLOGICAL SOCIETY

AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA

SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

PACIFIC COAST OBSTETRICAL AND GYNECOLOGICAL SOCIETY

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

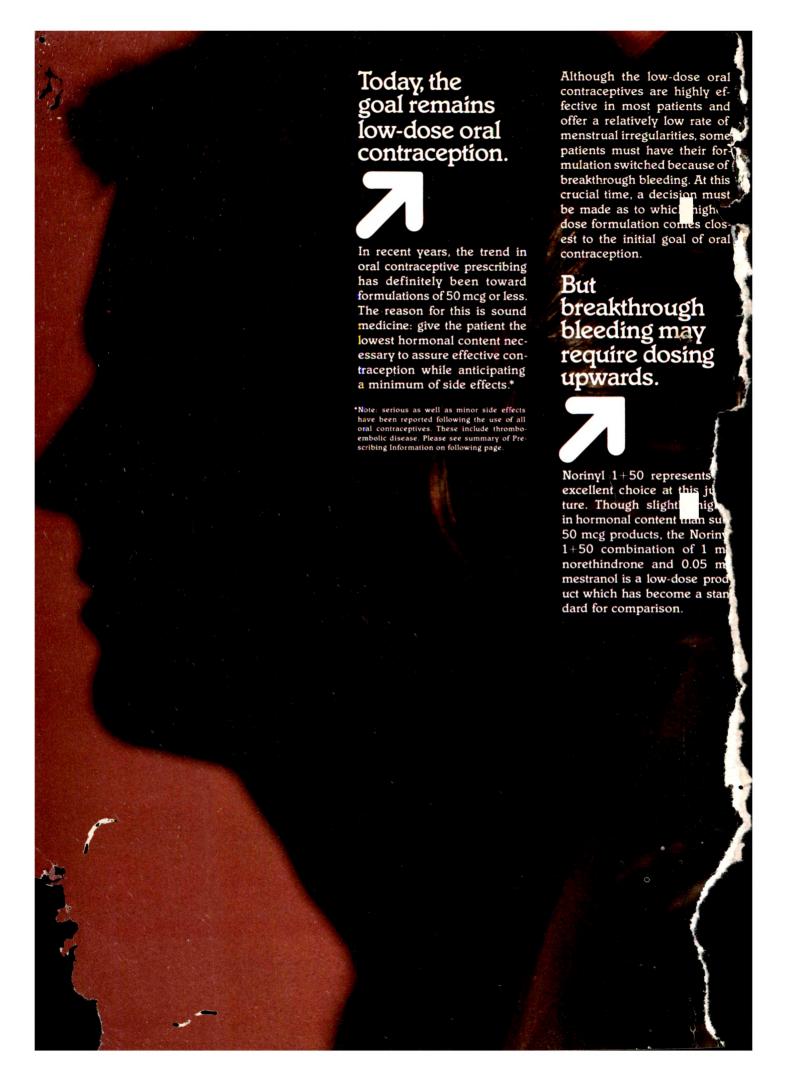
SOCIETY FOR GYNECOLOGIC INVESTIGATION

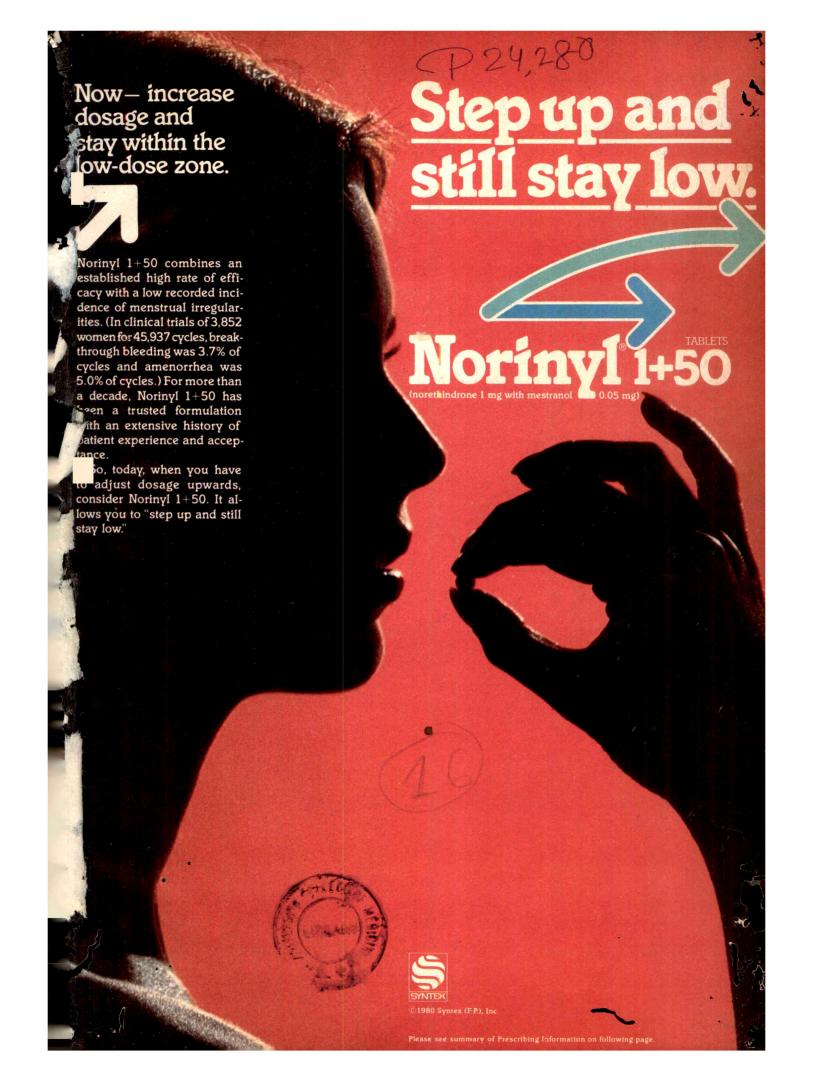




Published by

THE C. V. MOSBY COMPANY St. Louis, Missouri 63141





### Norinyl® 1+50 21-Day Tablets With mestranol 0.05 mg.) Norinyl® 1+50 28-Day Tablets (21 norethindrone 1 mg. with mestranol 0.05 mg. tablets followed by 7 inert tablets)

#### **ORAL CONTRACEPTIVE (O.C.) AGENTS**

INDICATIONS O.C.s are indicated for the prevention of pregnancy. DOSE-LATED RISK OF THROMBOEMBOLISM FROM O.C.s. Studies have shown a positive association between the dose of estrogens in O.C.s and the risk of thomboembolism. For this reason, it is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The O.C. product prescribed for any given patient should be that product which contains the uct prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance. It is recommended that new acceptors of O.C.s. should be started on preparations containing 0.05 mg or less of estrogen. should be started on preparations containing 0.05 mg or less of estroger CONTRAINDICATIONS 1. Known or suspected pregnancy (see Warning No. 5). 2. Thrombophlebitis or thromboembolic disorders. 3. A past history of deep viein thrombophlebitis or thromboembolic disorders. 4. Undiagnose abnormal genital bleeding, 5. O.C.s should not be used by women who have o have had any of the following conditions: a. Cerebral vascular or coronary a tary disease. b. Known or suspected carcinoma of the breast. C. Known o suspected estrogen dependent neoplasia. d. Benign or malignant liver tumo which developed during the use of oral contraceptives or other estrogen containing products.

WARNINGS: Cigarette smoking increases the risk of serious car-diovascular side effects from 0.C. use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use 0.C.s should be strongly advised not to smoke.

The use of O.C.s is associated with increased risk of several serious c tions including thromboembolism, stroke, myocardial infarction, liver tumor, gall bladder disease, visual disturbances, fetal abnormalities, and hypertension. Practitioners prescribing O.C.s should be familiar with the following information relating to these risks.

1. Thromboembolic Disorders and Other Vascular Problems: An increased risk of thromboembolic and thrombotic disease associated with the use of 0.C.s is well established. One British study demonstrated an increased relative risk for fatal venous thromboembolism: two British and three American studies demonstrated an increased relative risk for fatal venous thromboembolism: two British and three American studies demonstrated an increased relative risk for non-fatal venous thromboembolism. These studies estimate that users of 0.C.s are 4 to 11 times more likely than nonusers to develop these diseases without evident cause. CEREBROVASCULAR DISORDERS. Two American studies demonstrated an increased relative risk for stroke, which had not been shown in prior British studies. In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of hemorrhagic stroke was 2.0 times greater in users and the relative risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers. A British long-term, follow-up study reported in 1976 a highly significant association between 0.C. use and stroke. Another British long-term, follow-up study had suggested such an association in 1974, but the number of cases was too small to estimate the risk. MYOCAROIJAL INFARCTION. An increased relative risk of myocardial infarction associated with the use of 0.C. s. has been reported. confirming a previously suspected association. One study conducted in the United Kingdom found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of precisiposing condition to myocardial infarction, regardless of whether the patient was an 0.C. user of not. 0.C.s. however, were found to be an additional risk factor. In terms of relative risk, that has been estimated that 0.C. users who do not smoke (smoking is considered a major predisposing . Thromboembolic Disorders and Other Vascular Problems: An increased Sitisfi vital statistics which show acute myocardial infarction death rates 2-to 3-times less than in the U.S. for women in these age groups; consequently actual U.S. death rates could be higher.) The importance of other predisposing conditions mentioned above in determining relative and absolute risks as not been quantified; other synergistic actions may exist. RISK OF DOSE. In an analysis of data derived from several national adverse reaction reporting systems. British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen were associated with a higher risk of thromboembolism than those containing 0.0. In mg or more of estrogen were associated with a higher risk of thromboembolism than those containing 0.00.8 mg of estrogen in the store of the containing of the store of the

LE 1. The annual number of deaths associated with control of fertility and

yomen are:	15-19	20-24	25-29	30-34	35-39	40-44
No method	5.6	6.1	7.4	13.9	20.8	22.6
Abortion only	1.2	1.6	1.8	1.7	1.9	1.2
Pill wy -nonsmokers	1.3	1.4	1.4	2.2	4.5	7.1
Pill (V -smokers	1.5	1.6	1.6	10.8	13.4	58.9
IDS only	0.9	1.0	1.2	1.4	2.0	1.9
contaception only radional contra-	1.1	1.6	2.0	3.6	5.0	4.2
eption and abortion	0.2	0.2	0.3	0.3	0.3	0.2

The risk of thromboembolic and thrombotic disease associated with 0.C.s. increases with age after approximately age 30 and myocardial infarction, is further increased by hypertension, hypertendemias, obesity, diabetes, or bistory of preciampic toxemia and especiamy by cigarette smoking. Based on

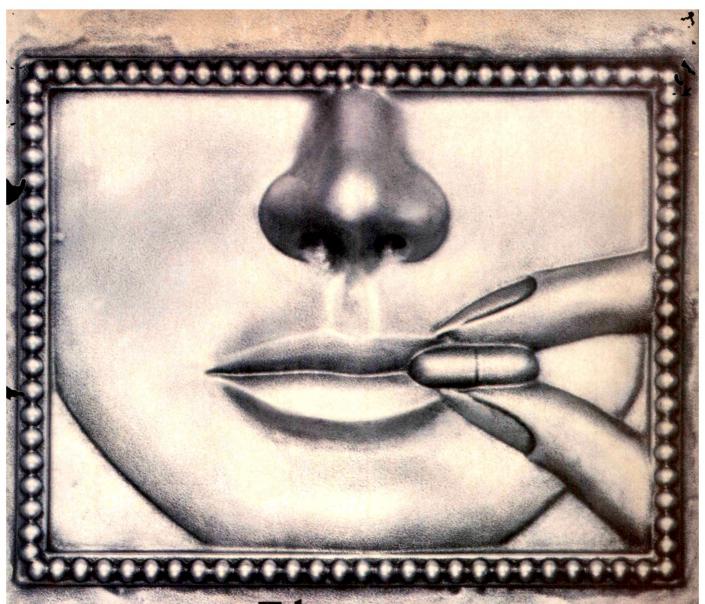
the data currently available, the following table gives a gross estimate of the risk of death from circulatory disorders associated with the use of 0.C.s: TABLE 2. Smoking habits and other predisposing conditions – risk associated with use of 0.C.s.

Age	Below 30	30-39	40+
Heavy smokers	C	В	A B
Light smokers	D	C	В
Nonsmokers		0.0	
(No predisposing conditions) Nonsmokers	U	C,D	C
(other predisposing conditions)	C	C,B	B,A

Use associated with very high risk. C—Use associated with moderate risk.
 Use associated with high risk. D—Use associated with low risk.

A—Use associated with very high risk. C—Use associated with moderate risk. B—Use associated with high risk. D—Use associated with high risk. D—Use associated with low risk. The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombosic disorders (e.g., thrombophiebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A four- to six-fold increased risk of post-surgery thromboembolic complications has been reported in 0.C. users. If feasible, 0.C.s should be discontinued at least 4 weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization. Data also suggest that the presence of varicose veins substantially increases the risk of superficial venous thrombosis of the leg, the risk depending on the severity of the varicosities. Ocular Lessions: There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with the use of 0.C.s. Discontinue 0.C. medication if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions; and institute appropriate diagnostic and therapeutic measures. Carcinoma. Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the incidence of mammary nodules, benign and malignant, in dogs. Several retrospective case-control studied in 0.C.s. have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs. Several retrospective case-control studied in 0.C.s. have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs. Several retrospective case-control studied in 0.C.s. of estogeneral relative risk (3.1 to 13.9 times) associating endometrial carcinoma with the prolonged use of estrogenties assess unb users with documented beingin irleast usease and or long-rein tell your users. One other study indicated an increasing risk of breast cancer in women taking menopausal estrogens, which increased with duration of follow-up. A reduced occurrence of benign breast tumors in users of 0.C.s has been well documented. In a prospective study of women with cervical dysplasia, there documented. In a prospective study of women with cervical dysplasia, there was an increase in severity and of conversion to cancer in situ in 0.C. users compared with nonusers. This became statistically significant after 3 to 4 years of use. Nonreversal of dysplasia within the first 6 months of pill use was suggested to be predictive of progression after prolonged exposure. There have been other reports of microglandular hyperplasia of the cervix in users of 0.C.s. In summary, there is at present no confirmed evidence from human studies of an increased risk of cancer associated with 0.C.s. Close clinical surveillance of all women taking 0.C.s. is, nevertheless, essential. In all cases of undiagnostic persistent or recurrent shorourgh appropria surveillance of all women taking 0.C.s. is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use 0.C.s. shiead of other methods of contraception. 4. Liver Tumors: Sudden severe abdominal pain or shock may be due to rupture care if they elect to use 0.C.s instead of other methods of contraception. 4. Liver Tumors. Sudden severe abdominal pain or shock may be due to rupture and hemorrhage of a liver tumor. There have been reports associating benign or malignant liver tumors with 0.C. use. This has been reported in short-term as well as long-term users of 0.C.s. One study reported that use of 0.C.s with high hormonal potency and age over 30 years may further increase a woman's six of hepatocellular adenoma. Two studies relate risk with duration of use, the risk being much greater after 4 or more years of use. Although it is an uncommon lesion, it should be considered in women presenting with an "acute abdomen". The tumor may cause serious or fatal hemorrhage. Patients with liver tumors have demonstrated variable clinical features which may make liver tumors have demonstrated variable clinical features which may make preoperative diagnosis difficult. Some cases presented because of right upper quadrant masses, while most had signs and symptoms of acute in trapertioneal hemorrhage. Boutine radiological and laboratory studies may not be helpful. Liver scans may clearly show a focal defect. Hepatic arteriog raby may be a useful procedure in diagnosing primary liver neoplasm. 5: 
Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and 
Maignancy in Female Offspring: The use of female sex hormones —both estrogenic and progestational agents — during early pregnancy may seriously 
damage the offspring. It has been shown that females exposed in utero to 
diethylstilbestrol. a nonstercidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely 
rare. This risk has been estimated to be of the order of 1 in 1,000 exposures 
or less. Although there is no evidence at the present time that 0. C. S further 
enhance the risk of developing this type of malignancy, such patients should 
be monitored with particular care if they elect to use 0. C.s instead of other 
methods of contraception. Furthermore, a high percentage of women exposed to diethylstilbestrol (from 30 to 90%) have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal 
malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with the use of other estrogens, it cannot be presumed that they would not induce similar changes. 
An increased risk of congenital anomalies, including heart defects and limb 
defects, has been reported following use of sex hormones, including 0.C. s., 
in pregnancy. In one case-control study it was estimated that there was a 
4.7-fold increased relative risk of limb-reduction defects in infants exposed in 
utero to sex hormones (O.C. s. hormonal withdrawal tests for pregnancy or 
attempted treatment for threatened abortion). Some of these exposures were 
very short and involved only a few days of treatment. The data suggest that 
the risk of limb-reduction defects in exposed for these including 0.C.s., 
during early pregnancy occurred at a rate raphy may be a useful procedure in diagnosing primary liver neoplasm. Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, a Malignancy in Female Offspring: The use of female sex hormones—both apprised of the potential risks to the fetus and the advisability of continuating of the pregnancy should be discussed in the light of these risks. It is also recommended that women who discontinue 0.C.s with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this recommendation. The administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of

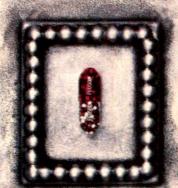
pregnancy, 6. Gall Bladder Disease. Studies report an increased risk of gall bladder disease in users of 0.C.s or estrogens. In one study, an increaser risk appeared after 2 years of use and doubled after 4 or 5 years of use. I another study an increased risk was apparent between 6 and 12 months or use. 7. Carbohydrate and Lipid Metabolic Effects: A decrease in glucose the erance has been observed in a significant percentage of patients on 0.C. for this reason, prediabetic and diabetic patients should be carefully conserved while receiving 0.C.s. An increase in triglycerides and total pholipids has been observed in patients receiving 0.C.s. The clinical significance of this finding is unknown. 6. Elevated Blood Pressure: An increase in blood pressure has been reported with 0.C. use. In the first year use, the prevalence of women with hypertension is low in users and may no higher than that of a comparable group of nonusers. The prevalencing users increases, however, with longer exposure, and in the fifth year of users increases, however, with longer exposure, and in the fifth year of users increases, however, with longer exposure, and in the fifth year of users with the development of hypertension in 0.C. use. Women with a history of elevated blood pressure (hypertension) preexisting real activities of the pressure with group of toxemia or elevated blood pressure of presure with the development of hypertension in 0.C. use. Women with a history of elevated blood pressure (hypertension or its consequences, or a histor of excessive weight gain or fluid retention during the menstrual cycle may be used to the pressure with the development of hypertension in 0.C. use. Women with be grouped and of the cause of the pressure way remain within the "normal" range, the clinical implications of eyatic should be monitored closely. Even though elevated blood pressure with grouped to the pressure may or may not persist after discontinuation of the 0.C. Headache: The onset or exacerbation of migraine or development of headar of to be independent or the duration of use of the preparations. While pairment diminishes with time, there is still an appreciable difference in results in nulliparous women for the 0.C. and non-0.C. groups 30 month after discontinuation of birth control. For parous women the difference is a longer apparent 30 months after cessation of contraception. 12. Ectopic after discontinuation of birth control. For parous women the difference is a longer apparent 30 months after cessation of contraception. 12. Ectopia Pregnary: Ectopic as well as intrauterine pregnancy may occur in contract tive failures. However, in progestogen-only 0. C. failures, the ratio of ectops to intrauterine pregnancies is higher than in women who are not receiving 0.C.s, since the drugs are more effective in preventing intrauterine than topic pregnancies. 13. Breast Feeding; 0. C.s. given in the postpartum permay interfere with lactation. There may be a decrease in the quantity a quality of the breast milk. Furthermore, a small fraction of the hormon agents in 0.C.s has been identified in the milk of mothers receiving the drugs. The effects, if any, on the breast teld child have not been determined, feasible, the use of 0.C.s should be deferred until the infant has beweand. PRECAUTIONS EGNEFAAL 1. A complete medical and family history should be taken prior to the initiation of 0.C.s. The pretreatment and periodic hysical examinations should include special reference to blood pressure breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, 0.C.s should not be prescribed for longer than 1 year without another physical examination being performed. 2 Under the influence of estrogen-progestogen preparations, preexistive pressed while taking 0.C.s should stop the medication and use an alter method of contraception in an attempt to determine whether the sympto. drug related. 4. 0.C.s may cause some degree of fluid retention. They should be prescribed with caution, and only with careful montroing, in patients with a history of jaundice during pregnancy have increased risk of ecurrence of jaundice while receiving 0.C. therapy. If it dice develops in any patient receiving such drugs, the medication should iscontinued. 6. Steroid hormones may be poorly metabolized in patie with impaired liver function and should be administered with caution in st. patien increased risk of recurrence or jauntice white receiving U.S. inerapy. II increased incontinued. 6. Steroid hormones may be porty metabolized in patie with impaired liver function and should be administered with caution in st patients. 7. 0. C. users may have disturbances in normal tryptophmetabolism which may result in a relative pyridoxine deficiency. The clinic significance of this is unknown. 8. Serum folate levels may be depressed to C. C. therapy. Since the pregnant woman is predisposed to the developme. of folate deficiency and the incidence of folate deficiency increases with reasing gestation, it is possible that if a woman becomes pregnant shor after stopping 0. Cs. she may have a greater chance of developing folate ficiency and complications attributed to this deficiency. 9. The patholog should be advised of 0. C. therapy when relevant specimens are submitted. 10. Certain endocrine and liver function tests and blood components may affected by estrogen-containing 0. Cs. S. for example: a. Increased sulformophthalien retention. b. Increased prothrombin and factors VII. VIII. and X. decreased antithrombin 3: increased norepinephrine-induced plate aggregability. c. Increased thyroid binding globulin (T&G) leading to creased circulating total thyroid hormone, as measured by protein-bouriodine (PBI). 14 by column, or 14 by radiommunoassay. Free 13 resin uptais decreased, reflecting the elevated TBG, free 14 concentration is unaftered. Decreased pregnamediol exerction. e. Reduced response to metrytopic test. DRUG INTERACTIONS 0. Cs. may be rendered less effective by virtue of during interaction with rifampin, isoniazid, ampicillin, etracycline, neomycin, pen civilin v. chioramphenicol, sufforamineses, introduration, barbiturates, pheny toin, primidone, analgesics, tranquilizers, and antimigratine preparations. O. c. may after the effectiveness of other types of drugs, such as oral anticoarilants, anticonvulsants, tricyclic antidepressants, antitivpertensive age (e.g., quanethidine), vitamins and hypoglycemi



# Taking iron shouldn't take an iron will.

For many patients who need iron supplementation, gastric distress can interfere with compliance. But it shouldn't be a problem with Feosol® Spansule® Capsules.

Feosol provides iron in its most easily
absorbed (bivalent) form, as ferrous sulfate. In
Spansule Capsules, the iron is divided among
controlled-release pellets that disperse over a
large area of the gastric mucosa, resulting in
minimal distress and therefore better patient
compliance. And studies\* show that iron from



Spansule Capsules is absorbed as completely as iron from elixir.

Feosol is the brand of iron supplementation most often recommended by physicians for iron deficiency and iron-deficiency anemia. It can make your patients' compliance problems a thing of the past. Ask your Smith Kline & French Representative for samples.



Professional Products Division
a SmithKline company

# PAGE SPANSULE CAPSULES

PURE AND SIMPLY NO. 1.

Feosol Spansule Capsules, bottles of 30/Feosol Tablets, bottles of 100/Feosol Elixir, bottles of 12 fl. oz.

\*Data on file, Professional Products Division.

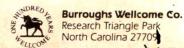
As CLOSE AS A CLASSIC CAN COME TO THE FUTURE.

Aspirin and codeine. Classic agents whose respective roles in medicine continue to be developed. Empirin® c Codeine. An impressive history and an important future.

Each tablet contains: aspirin, 325 mg; plus codeine phosphate in one of the following strengths: No. 2—15 mg, No. 3—30 mg, and No. 4—60 mg. (Warning—may be habit-forming.)







# American Journal of Obstetrics and Gynecology

Copyright © 1980 by The C. V. Mosby Company

**Contents** 

# September 1

1980

### **Obstetrics**

#### Postural blood pressure differences in pregnancy

-

P. W. J. Van Dongen, M.D., T. K. A. B. Eskes, M.D., C. B. Martin, M.D., and M. A. Van 't Hof, Ph.D.

Nijmegen, The Netherlands

### Hemodynamic observations in evacuation of molar pregnancy

6

David B. Cotton, M.D., Steven G. Bernstein, M.D.,

John A. Read, M.D., Lieutenant Colonel, MC, USA, Thomas J. Benedetti, M.D.,

Gerrit D'Ablaing, M.D., Frank C. Miller, M.D., and C. Paul Morrow, M.D.,

with the technical assistance of Gary M. Flynn

Los Angeles, California

(Contents continued on page 7)

Vol. 138, No. 1, September 1, 1980. The American Journal of Obstetrics and Gynecology is published semimonthly by The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141. POSTMASTER: Send address changes to above address.

1980 Annual subscription rates	U.S.A.	Foreign countries (surface mail) All regions	Region 1	Foreign countries (airmail)* Region 2	Region 3
Institutional†	\$52.50	\$72.50	\$101.45	\$132.65	\$163.85
Individual‡	\$35.50	\$55.50	\$ 84.45	\$115.65	\$146.85
Student, resident‡	\$28.40	\$48.40	\$ 77.35	\$108.55	\$139.75

Single copies are \$4.50 postpaid. Remittances should be made by check, draft, or post office or express money order payable to this JOURNAL.

\*Airmail breakdown—Domestic: First-class and Priority rates for the U.S. and possessions are available upon request. Region 1. Central America, islands, and mainland colonies of European countries in The Americas. Region 2: South America, Europe, Egypt, Africa (bordering the Mediterranean). Region 3: Asia, Australasia, Africa (other than Mediterranean), Middle East, Far East, The Pacific, U.S.S.R. (and constituent Republics).

†Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics; city, county, state, provincial, and national government bureaus and departments; and all commercial and private institutions and organizations.

‡Personal subscriptions and all student-rate subscriptions must be in the names of, billed to, and paid by individuals. All student-rate requests must indicate training status and name of institution.

Subscriptions may begin at any time.

Second-class postage paid at St. Louis, Missouri, and additional mailing offices, Printed in the U.S.A. Copyright © 1980 by The C. V. Mosby Company.



# The only system that lets two surgeons and two cameras work together.

# Dual stereoscopic viewing.

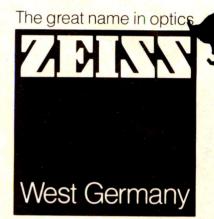
The Zeiss Operation Microscope 7-P/H is designed so two surgeons can work face-to-face. A 1:5 zoom system affords continuous, motorized magnification change. The slim body gives free view of the surgical area. Vertical position guarantees depth of focus over the entire field (not possible with inclined microscopes). The 7-P/H can be rotated through 360°, and offers a choice of several working distances. Of course, the superior Zeiss optics are unequaled for sharp definition and color rendition.

# Simultaneous TV and still-camera use.

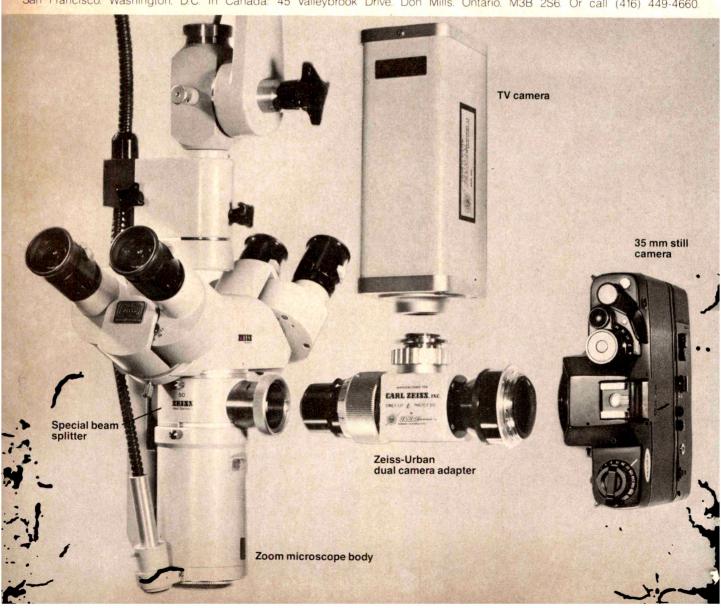
The Vertolux P/H fiber optic illumination system is so bright that two recording systems, e.g. TV and still camera, can be used simultaneously via the unique Zeiss-Urban dual camera adapter which attaches to the Zeiss beam splitter. Because the beam splitter functions right through the optical system of the microscope, the field of view is exactly as the surgeon sees it.

For further information on this or other Zeiss microscopes, write to us.

Nationwide service.



Carl Zeiss, Inc., 444 5th Avenue, New York, N.Y. 10018 (212) 730-4400. Branches: Atlanta. Boston. Chicago. Houston. Los Angeles. San Francisco. Washington. D.C. In Canada: 45 Valleybrook Drive. Don Mills. Ontario. M3B 2S6. Or call (416) 449-4660.



# Contents continued from page 5

Acceptance of amniocentesis by low-income patients in an urban hospital	11
Janet P. Marion, M.S., Gulzar Kassam, M.D., Paul M. Fernhoff, M.D.,	
Karlene E. Brantley, M.N., Linda Carroll, M.N., June Zacharias, M.N., Luella Klein, M.D.,	
Jean H. Priest, M.D., and Louis J. Elsas II, M.D.	
Atlanta, Georgia	
Myomas of the uterus in pregnancy: Ultrasonographic follow-up	16
David Muram, M.D., Martin Gillieson, M.B., F.R.C.S.(C.), and Jack H. Walters, M.D.	
Ottawa, Ontario, Canada	
Plasma oxytocin levels and disappearance rate after buccal Pitocin	20
M. Yusoff Dawood, M.D., M.Med., M.R.C.O.G., F.A.C.O.G.,	
Oliva Ylikorkala, M.D., Dr.med., and Fritz Fuchs, M.D., Dr.med., F.A.C.O.G.	
Chicago, Illinois, and New York, New York	
Analysis of amniotic fluid, maternal plasma, and cord blood for a human breast	25
gross cystic disease fluid protein	
Darrow E. Haagensen, Jr., M.D., Ph.D., Stanley A. Gall, M.D., Jane E. Brazy, M.D.,	
Jan Giannola, R.N., and Samuel A. Wells, Jr., M.D.	
Durham, North Carolina	
Fetus, placenta, and newborn	
Biophysics of the developing heart. I. The force-interval relationship	33
Page A. W. Anderson, Andrés Manring, and Carlyle Crenshaw, Jr.	
Durham, North Carolina	
Biophysics of the developing heart. II. The interaction of the force-interval	44
relationship with inotropic state and muscle length (preload)	
Page A. W. Anderson, Andrés Manring, and Carlyle Crenshaw, Jr.	
Durham, North Carolina	
Midtrimester abortion induced by hyperosmolar urea and prostaglandin F <sub>2α</sub> in	55
patients with previous cesarean section: Clinical course and potential for	
uterine rupture	
Milagros F. Atienza, M.D., Ronald T. Burkman, M.D., and Theodore M. King, M.D., Ph.D.	
Baltimore, Maryland	
Umbilical blood flow response to embolization of the uterine circulation	.60
James F. Clapp III, M.D., Hazel H. Szeto, M.D., Ph.D., Rødney Larrow, Jean Hewitt, and	1
Leon I. Mann, M.D.	
Burlington, Vermont	
Characterization of triacylglycerol lipase activity in human amniotic fluid	68
Charles Merger, Anne Valette, Henri Ruf, and Jean Boyer	
Marseille, France .	
(Contents continued	(O page 0)



# SENOKOT'S

(standardized senna concentrate and dioctyl sodium sulfosuccinate)

Tablets



# the "S" stands for softener

### For patients with hard, dry stools

Hard, dry stools hurt, and may be hazardous by causing straining. SENOKOT-S Tablets offer comfortable relief by softening the stool and stimulating its movement.

# Provides standardized senna concentrate, a clinically established laxative of choice

Standardized senna concentrate is a gentle, effective neuroperistaltic stimulant with documented effectiveness in thousands of patients. Its virtually colon-specific, gentle, predictable action is generally free of side effects at proper dosage levels.

### Provides DSS, the classic stool softener

DSS in SENOKOT-S Tablets complements the laxative effect of standardized senna concentrate by "moistening" and softening the stool for smoother and easier passage.

### Comfortable overnight action

With DSS and standardized senna concentrate, SENOKOT-S Tablets provide *both* softness and stimulation for constipated patients with hard, dry stools. Taken at bedtime, SENOKOT-S Tablets usually induce predictable, comfortable evacuation the next morning.

### **Purdue Frederick**

# Contents continued from page 7

# **Gynecology**

Late recurrences of gestational trophoblastic neoplasia	73
Thomas C. Vaughn, M.D., Earl A. Surwit, M.D., and Charles B. Hammond, M.D.	
Durham, North Carolina	
Thyroid function in gestational trophoblastic neoplasia: Evidence that the	77
thyrotropic activity of chorionic gonadotropin mediates the thyrotoxicosis of	
choriocarcinoma	
Bruce C. Nisula, M.D., and George S. Taliadouros, M.D.	
Bethesda, Maryland	
Tubal lesions subsequent to sterilization and their relation to fertility after attempts	86
at reversal	
Gloria Vasquez, M.D., Robert M. L. Winston, M.D., M.R.C.O.G., Willy Boeckx, M.D., and	
Ivo Brosens, M.D., Ph.D.	
Leuven, Belgium	
Receptor-like binding proteins for testosterone and progesterone in the	93
human ovary	
Ariel Milwidsky, M.D., Muazaz A. Younes, Ph.D., Norma F. Besch, Ph.D.,	
Paige K. Besch, Ph.D., and Raymond H. Kaufman, M.D.	
Houston, Texas	
The use of medroxyprogesterone acetate for relief of climacteric symptoms	99
John C. Morrison, M.D., Dan C. Martin, M.D., Richard A. Blair, M.D.,	
Garland D. Anderson, M.D., Bradford W. Kincheloe, M.D., G. William Bates, M.D.,	
James W. Hendrix, M.D., Michel E. Rivlin, M.D., Evelyn K. Forman,	
Maureen G. Propst, M.N., R.N., and Robert Needham, M.S.	
Memphis, Tennessee, Jackson, Mississippi, and Kalamazoo, Michigan	
Comment developments	

# **Current developments**

The obstetrician's opportunity: Translating "breast is best" from theory to practice

Beverly Winikoff, M.D., M.P.H., and Edward C. Baer, B.A.

New York, New York

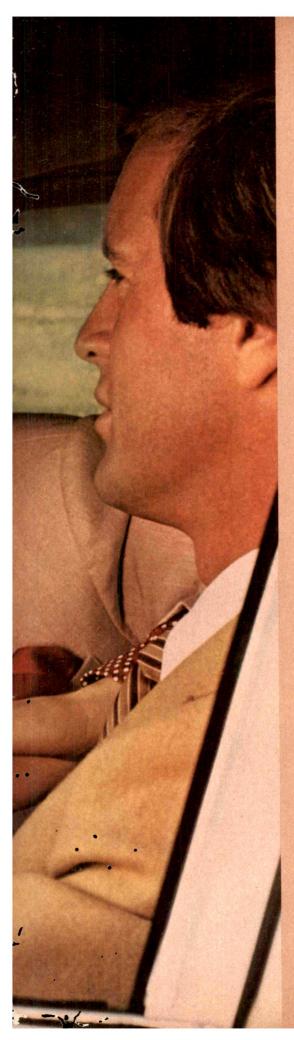
# **Items**

Items 118

Information for authors on page 19

Index to advertisers on page 40





# LOESTRIN 1.5/30

(1.5 mg norethindrone acetate and 30 mcg ethinyl estradiol tablets, USP)

...He says there's no sense taking more estrogen than you need."

LOESTRIN\*1.5/30 limits estrogen exposure and often reduces the frequency of estrogen-related side effects, because it contains just 30 mcg of ethinyl estradiol. LOESTRIN 1.5/30 combines this low estrogen dose with norethindrone acetate, a progestin that's been used alone for years in gynecologic therapy. Together, they offer more than 99% effective oral contraception.

When you're considering starting new patients on the "pill" or switching patients from higher estrogen-containing OCs to the low-dose ones, consider LOESTRIN 1.5/30...available in a 21-day regimen and the convenient 28-day regimen which includes 7 days of iron tablets to take during the "off-week" and simplifies remembering to take the medication.

LOESTRIN 1.5/30...highly effective protection with limited estrogen exposure

Please see following page for prescribing information.

PARKE-DAVIS

Div of Warner-Lambert Co Morris Plains, NJ 07950 USA

#### ef Summary of Prescribing Information LOESTRIN® 1.5/30

indrone acetate and 30 mcg ethinyl estradiol tablets, USP) See section under on Administration and How Supplied.

#### -DESCRIPTION

Loestrin 1.5/30 Products are progestogen-estrogen combinations. INDICATION AND USAGE

oestrin 1.5/30 Products are indicated for the prevention of pregnancy in women who elect to use oral contracentives

In clinical trials with Loestrin 1.5/30 involving 17,139 therapy cycles, there was a pregnancy te of 0.49 per 100 woman years.

Pose-related risk of thromboembolism from oral contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable prepared to the product which contains the least amount of estrogen that is compatible with an acceptable rate and patient acceptance

#### CONTRAINDICATIONS

- INTRAINDICATIONS
  Thrombophilebitis or thromboembolic disorders
  A past history of deep-vein thrombophilebitis or thromboembolic disorders
  Cerebral vascular or coronary artery disease
  Known or suspected carcinoma of the breast
  Known or suspected estrogen-dependent neoplasia

- Undiagnosed abnormal genital bleeding
   Known or suspected pregnancy (See No. 5 under WARNINGS.)

#### WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age.

women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma gallbladder disease, and hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

Thromboembolic Disorders and Other Vascular Problems: An increased risk of thromboem-

1. Thromboembolic Disorders and Other Vascular Problems: An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established. Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic.

Cerebrovascular disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater.

Myocardial infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association. These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor. whether the patient was an oral contract found to be a clear additional risk factor.

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke. The amount of smoking is also an important factor.

flisk of dose: In an analysis of data. British investigators concluded that the risk of throm-boembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives; however, the quantity of estrogen may not be the sole factor involved. Estimate of excess mortality from circulatory diseases: The risk of diseases of the circula-tory system is concentrated in older women, in those with a long duration of use, and in ciga-rattle smokers. rette smokers

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke. The risk of thromboemboic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypercholesterolemia, obesity, diabetes, or history of preeclamptic taxemia, and especially by cigarette smoking.

toxemia, and especially by cigarette smoking.

The physician and the patient should be alert to the earliest manifestations of thromboem bolic and thrombotic disorders. Should any occur or be suspected, the drug should be discontinued immediately.

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

2. Ocular lesions: Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision; onset of proptosis or diplopa; papilledema, or retinal vascular lesions.

3. Carcinoma: Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver. In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported. However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination of projections and projections.

evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives.

Studies found no evidence of increase in breast cancer in women taking oral contraceptives; however, an excess risk in users with documented benign breast disease was reported. There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of users is, nevertheless, essential. In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care.

who have breast nodules, fibrocystic disease, or abnormal mammograms, should be mornioned with particular care.

4. Hepatic Tumors: Benign hepatic adenomas have been found to be associated with oral contraceptives. Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. Usage in or immediately Preceding Pregnancy: Birth Defects in Offspring, and Malignancy in Female Offspring. During early pregnancy, female sex hormones may seriously damage the offspring.

offspring.

An increased risk of congenital anomalies, including heart defects and limb defects, has

An increased risk of congenital anomalies, including heart defects and limb defects, has been anorted with the use of oral contraceptives in pregnancy.

There is some evidence that friploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives. Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods. If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed.

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive. Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. Gallbladder Disease: Studies report an increased risk of surgically confirmed gallbladder.

disease in users of oral contraceptives.

7. Carbohydrate and Lipid Metabolic Effects: Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be

observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed.

B. Elevated Blood Pressure: An increase in blood pressure has been reported in patients receiving oral contraceptives. The prevalence in users increases with longer exposure, Age is also strongly correlated with development of hypertension. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure.

9. Headache: Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives.

10. Bleeding Irregularities: Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, nonfunction causes should be borne in mind. In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy.

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives.

Ectopic Pregnancy: Ectopic as well as intrauterine pregnancy may occur in contraceptive

12. Breast Feeding: Oral contraceptives may interfere with lactation. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers received these drugs. drugs.

#### PRECAUTIONS

PRECAUTIONS

1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.

2. Preexisting uterine leiomyomata may increase in size.

3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

4. Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice. If jaundice develops, the medication should be discontinued.

6. Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function.

7. Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency.

relative pyridoxine deficiency.

8. Serum folate levels may be depressed.

9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted.

are submitted

10. Certain endocrine and liver function tests and blood components may be affected.

(a) Increased sulfobromophthaliein retention. (b) Increased prothrombin and factors VII, VIII,

IX, and X: decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

(c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid
hormone. (d) Decreased pregnanediol excretion. (e) Reduced response to metryapone test.

Drug interactions: Reduced efficacy and increased incidence of breakthrough bleeding have
been associated with concomitant use of rifampin and an association has been suggested with
barbiturates, phenylbulazone, openytoin sodium, and ampicillin. phenylbutazone, phenytoin sodium, and ampicillin.

#### ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with oral contraceptives.

contraceptives.
Thrombophlebitis, Pulmonary embolism; Coronary thrombosis; Cerebral thrombosis;
Cerebral hemorrhage; Hypertension; Gallbladder disease; Benign hepatomas, Congenital

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed. Mesenteric thrombosis

contraceptives, although additional confirmatory studies are needed. Mesenteric thrombosis, Neuro-ocular lesions, eg. retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: gastrointestinal symptoms; breakthrough bleeding; spotting; change in menstrual flow; dysmenor-rhea; amenorrhea during and after treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma; breast changes; change in weight; change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately post partum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidasis; change in corneal curvature; intolerance to contact lenses.

The following adverse reactions have been reported and the association has been neither.

The following adverse reactions have been reported and the association has been neither confirmed nor refuted.

Premenstrual-like syndrome; cataracts; changes in libido; chorea; changes in appetite; cystitis-like syndrome; headache; nervousness; dizziness; hirsutism; loss of scalp hair; ythema multiforme, erythema nodosum; hemorrhagic eruption; vaginitis, porphyria.

cystins-like syntomic; headache; hervoushess, utzness, manager and south hospitals.

Special Notes on Administration

Loestrin [21] 1.5/30 (1.5 mg norethindrone acetate and 30 mcg ethinyl estradiol tablets, USP)—Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication.

Loestrin [E] 1.5/30—Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after the brown ferrous fumarate tablets have been started.

Because of the relatively low estrogenic content, Loestrin 1.5/30 is not a good cyclic regulator. There are patients whose inherent hormone balance will require larger amounts of estrogen than that contained in Loestrin 1.5/30 to achieve cyclic regularity. These patients experience altered bleeding patterns, which do not conform to treatment schedules.

The physician should be alert to the fact that the irregular bleeding patterns could mask bleeding from organic cause, and appropriate diagnostic measures should be taken if the bleeding persists or continues after changing to a higher estrogen-content product. After several months, bleeding may be reduced to a virtual absence; reduced flow may be a result of medication and not indicative of pregnancy.

nedication and not indicative of pregnancy.

#### HOW SUPPLIED

Loestrin [Eq. 1.5/30 is available in compacts each containing 21 green tablets and 7 brown tablets. Each green tablet contains 1.5 mg of norethindrone acetate and 30 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous furnarate. Available in packages of five

compacts and packages of five refills.

Loestrin 21 1.5/30 is available in compacts each containing 21 tablets. Each green tablet contains 1.5 mg of norethindrone acetate and 30 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills

**PARKE-DAVIS** 

Div of Warner-Lambert Co

### **Editors**

JOHN I. BREWER, Editor in Chief

FREDERICK P. ZUSPAN, E. J. QUILLIGAN, Editors

ALBERT B. GERBIE, Associate Editor

HOWARD C. TAYLOR, JR., ALLAN C. BARNES, Emeritus Editors

# Advisory committee on policy

C. D. Christian

Leo J. Dunn

David Figge
Fred T. Given

A. Brian Little

Edgar L. Makowski

George D. Malkasian

Roy T. Parker

W. Ann Reynolds

J. C. G. Whetham

# **Board of corresponding editors**

Oscar Aguero, Caracas
Frederick Kubli, Heidelberg
Pierre O. Hubinont, Brussels
Malcolm Symonds, Nottingham
Ichiro Taki, Fukuoka



# **If she** could cope, she wouldn't have called.

# Vasomotor The severity of vaso-

symptoms motor symptoms is notoriously variable.

So is the individual patient's reaction to them. What is viewed as a passing annoyance by one may be incapacitating to another.

When should estrogen replacement therapy be initiated?

First, moderate to severe flushes and sweats are a good indicator. But in addition, consider the •problem that brought her to you in the first place: her ability to cope with these vasomotor symptoms—or, more accurately, the lack of her

ability to cope. Finally, determine the absence of contraindications to estrogen therapy. For these women the high rate of effectiveness of PREMARIN (Conjugated Estrogens Tablets, U.S.P.) against vasomotor symptomatology remains unchallenged.

In most cases the patient who should be helped can be helped - with careful attention to dosage. regimen, and follow-up—until the period of physiologic adjustment to low endogenous estrogen levels is complete.

PREMARIN.

The proven therapy many women need.

Vasomotor symptoms beyond counseling... well within the reach of

PREMARIN (CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg/0.625 mg/1.25 mg/2.5 r

#### 1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. "3 This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade." The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment' and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration." It therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early reponancy. Three independent case control studies have reported an increased risk of endome

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rate.<sup>5,6</sup> This risk has been estimated as not greater than 4 per 1000 exposures.<sup>6</sup> Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis.<sup>6,-12</sup> epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.<sup>13,-16</sup> One case control study <sup>16</sup> estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy or in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

**DESCRIPTION:** PREMARIN (Conjugated Estrogens Tablets, U.S.P) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and  $17\alpha$ -dihydroequilin, together with smaller amounts of  $17\alpha$ -estradiol, equilenin, and  $17\alpha$ -dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences — National Research Council and/or other information. FDA has classified the cations for use as follows:

- Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.
- Atrophic vaginitis
   Kraurosis vulvae.
- 4. Female hypogonadism
- Female castration
- Primary ovarian failure.

  Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.

metastatic disease.

8. Prostatic carcinoma – palliative therapy of advanced disease.

9. Postpartum breast engorgement – Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens. PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the tollowing conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, 19 although a recent study has gaised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

surgically confirmed gallbladder disease in women receiving postmenopausal estrogens. 
Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. 
""-22" Users of oral contraceptives have an increased risk of diseases, such as thrombophiebitis, pulmonary embolism, stroke, and rayocardial infarction. 
"21-30" Cases of retinal thrombosis, mesenteric thrombosis, and optic neutrins have been reported in oral contraceptive users. 
"">-37 An increased risk of postsurgery thromboembofic complications has also been reported in users of oral contraceptives. 
"11-31" Heasible, estrogen should be discontinued at least 4 weeks before surgery of the place of the post of the place of th

artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown<sup>35</sup> to increase the risk of nonfratal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a

Benign hepatic adenomas should be considered in estrogen users having abdominal pain Benign nepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. <sup>36</sup> Increased blood pressure may occur with use of estrogens in the menopause. <sup>37</sup> and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast e metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hyperglenging or in young natients in when bone growth is not diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

complete.

The following changes may be expected with larger doses of estrogen:
a. Increased sulfobromophthalein retention.
b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

- d. Impaired glucose tolerance.
  e. Decreased pregnanediol excretion.
  f. Reduced response to metyrapone test.
  g. Reduced serum folate concentration.

g. Reduced serum folate concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome, amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum, hemorrhagic eruption; loss of scalp hair, hirsutism; steepening of corneal curvature; intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

porphyria: edema: changes in libido

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION: 1. Given cyclically for short term use only: For treatment of moderate to severe vasomotor symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. Given cyclically: Female hypogonadism. Female castration. Primary ovarian failure.

Osteoporosis
Female hypogonadism — 2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium. If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P), 2.5 to 7.5 mg daily in divided doses, for 20 days, During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.
Female castration and primary ovarian failure—1.25 mg daily cyclically. Adjust upward or

resumed on the fifth day of bleeding. Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. Given for a few days: Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. Given chronically: Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily

Inoperable progressing breast cancer in appropriately selected men and postmenopausar omen—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and

appropriate measures taken to rule out malignancy in the event of persistent or recurring

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each purple tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each yellow tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867—Each red tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868—Each greentablet contains 0.3 mg in bottles of 100 and 1,000.

PHYSICIAN REFERENCES: 1. Ziel, H.K., et al.: N. Engl. J. Med. 293:1167-1170, 1975. 2. Smith, D.C., et al.: N. Engl. J. Med. 293:1164-1170, 1975. 3. Mack, T.M., et al.: N. Engl. J. Med. 294:1262-1267, 1976. 4. Weiss, N.S., et al.: N. Engl. J. Med. 294:1259-1262, 1976. 5. Herbst, A.L., et al.: N. Engl. J. Med. 294:1259-1262, 1976. 5. Herbst, A.L., et al.: N. Engl. J. Med. 284:399-399, 1971. 7. Lanier, A., et al.: Mayo Clin. Proc. 48.793-799, 1973. 8. Herbst, A., et al.: Obstet. Gynecol. 40:287-298, 1972. 9. Herbst, A., et al.: Amayo. Clin. Proc. 48.793-799, 1973. 8. Herbst, A., et al.: Obstet. Gynecol. 40:287-298, 1972. 9. Herbst, A., et al.: Obstet. Gynecol. 43:118-128, 1974. 12. Sherman, A.I., et al.: Obstet. Gynecol. 43:118-128, 1974. 12. Sherman, A.I., et al.: Obstet. Gynecol. 43:118-128, 1974. 12. Sherman, A.I., et al.: Obstet. Gynecol. 44:531-545, 1974. 13. Gal. I., et al.: N. Engl. J. Med. 292:697-700, 1974. 17. Boston Collaborative Drug Surveillance Program. N. Engl. J. Med. 290:15-19, 1974. 18. Hoover, R., et al.: N. Engl. J. Med. 295:401-405, 1976. 19. Daniel, D. G., et al.: Lancet 2:560, 1967. 20. The Veterans Administration Cooperative Urological Research Group: J. Urol. 985:16-522, 1967. 20. Raniar J.C.: Lancet 2:560, 1967. 20. The Contraceptives and Health, New York, Pitman Corp., 1974. 24. Imman, W.H.W., et al.: Br. Med. J. 2:193-199, 1968. 25. Vessey, M.P., et al.: Br. Med. J. 2:245-248,

Epidemiol. 7120/80 103:445-456, 1976.



# American Journal of Obstetrics and Gynecology

in addition to those listed on the front cover the Journal is the official publication of the following societies

OBSTETRICAL SOCIETY OF PHILADELPHIA

NEW YORK OBSTETRICAL SOCIETY

BROOKLYN GYNECOLOGICAL SOCIETY ST. LOUIS GYNECOLOGICAL SOCIETY NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY THE OBSTETRICAL AND GYNECOLOGICAL SOCIETY OF MARYLAND CHICAGO GYNECOLOGICAL SOCIETY CINCINNATI OBSTETRICAL AND GYNECOLOGICAL SOCIETY WASHINGTON GYNECOLOGICAL SOCIETY PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY BOSTON OBSTETRICAL SOCIETY LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY SEATTLE GYNECOLOGICAL SOCIETY ALABAMA ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS AKRON OBSTETRICAL AND GYNECOLOGICAL SOCIETY KANSAS CITY GYNECOLOGICAL SOCIETY CENTRAL NEW YORK ASSOCIATION OF GYNECOLOGISTS AND OBSTETRICIANS NEW JERSEY OBSTETRICAL AND GYNECOLOGICAL SOCIETY IOWA OBSTETRIC AND GYNECOLOGIC SOCIETY THE TEXAS ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS OKLAHOMA CITY OBSTETRICAL AND GYNECOLOGICAL SOCIETY MEMPHIS OBSTETRICAL AND GYNECOLOGICAL SOCIETY UTAH OBSTETRICAL AND GYNECOLOGICAL SOCIETY ROCHESTER OBSTETRICAL AND GYNECOLOGICAL SOCIETY ARKANSAS OBSTETRICAL AND GYNECOLOGICAL SOCIETY TENNESSEE STATE OBSTETRICAL AND GYNECOLOGICAL SOCIETY NEW YORK GYNECOLOGICAL SOCIETY PACIFIC NORTHWEST OBSTETRICAL AND GYNECOLOGICAL ASSOCIATION BUFFALO OBSTETRICAL AND GYNECOLOGICAL SOCIETY SAN FRANCISCO GYNECOLOGICAL SOCIETY JACKSON GYNECIC SOCIETY INDIANA OBSTETRICAL AND GYNECOLOGICAL SOCIETY THE MINNESOTA OBSTETRICAL AND GYNECOLOGICAL SOCIETY



# Welch Allyn introduces a light source... second only to the sun.

# The NEW Halogen Exam Lite™

Welch Allyn's new Halogen Exam Lite brings Halogen illumination out into the open for the first time.

It's perfect for offices and exam areas where accurate illumination is needed.

A general purpose illuminator that offers economy, efficiency, convenience, versatility, and all the benefits of Halogen lighting.

- □ HALOGEN ILLUMINATION—An intense Halogen lamp for brilliant light. 3,100°K, 3,500 ft. candles (37,500 lumens per sq. meter) at a distance of 4 in. (10 cm.), life 50 plus hours
- ☐ FIBER OPTICS—Obedient, yet flexible fiber optics yield even and cool illumination at the distal end.

  48 in. (122 cm.)
- ☐ LITE BOX—A cool and quiet lite box, no fan or noise, designed to complement any decor (UL and CSA approved)

- ☐ LENS SYSTEM—A small easy-touse lens focussing system for adjusting and concentrating the light spot
- ☐ SHEATH—A disposable, clean sheath that prevents contamination
- ☐ MODES OF USE—Mount on wall, exam table, desk or use as a portable unit mounted on a mobile stand
- ☐ EFFICIENT—Economically efficient; draws only 30 watts of power while providing the finest diagnostic lighting available

Contact your Welch Allyn dealer for a demonstration today!



Lighting the way since 1915

Welch Allyn, Inc. Skaneateles Falls, New York 13153





# American Journal of Obstetrics and Gynecology

Copyright © 1980 by The C. V. Mosby Company

Editors

John I. Brewer, Editor in Chief 710 North Fairbanks Court, Chicago, Illinois 60611

Frederick P. Zuspan, Editor

The Ohio State University, 410 W. 10th Ave., Columbus, Ohio 43210

#### Information for authors

Submission of contributions. Manuscripts should in general be sent to a particular Editor according to the following plan: If it is from the southeastern quadrant of the United States or from Canada, or if it has been presented before one of the official sponsoring societies, to Dr. Brewer; if from the northeastern quadrant (including Ohio), or if it is a Clinical Opinion or a Letter to the Editors, to Dr. Zuspan; if from the north central states, any of the United States west of the Mississippi, Hawaii, Alaska, or abroad, to Dr. Quilligan.

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following written statement, signed by one author: "The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C. V. Mosby Company in the event the work is published. The undersigned author warrants that the article is original, is not under consideration by another journal, and has not been previously published. I sign for and accept responsibility for releasing this material on behalf of any and all co-authors." Authors will be consulted, when possible, regarding republication of their material.

All articles published in this JOURNAL must be contributed to it exclusively. Articles previously published in another language are not acceptable.

It is assumed by the Editors that articles emanating from a particular institution are submitted with the approval of the requisite authority.

Articles dealing with human experimentation cannot be accepted unless the experiment was approved by the author's local Human Experimentation Committee.

Statements and opinions expressed in the articles and communications herein are those of the author(s) and not necessarily those of the Editor(s) or Publisher and the Editor(s) and Publisher disclaim any responsibility or liability for such material. Neither the Editor(s) nor the Publisher guarantee, warrant, or endorse any product or service advertised in this publication, nor do they guarantee any claim made by the manufacturer of such product or service.

Manuscripts. Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. The original and one copy of the manuscript are required. References should be placed at the end of the article. They should include name of author(s), article title, name of periodical, volume, page, and year. Name of periodical should conform to that shown in latest List of Journals Indexed in Index Medicus. For reference style see current issue of JOURNAL. Authors are encouraged to limit references to 16, except for Communications in Brief, limited to 2, Current Investigation and Clinical Opinion, limited to 6, and Current Developments, for which there is no limit. Illustrations accompanying manuscripts should be numbered, provided with suitable

#### E. J. Quilligan, Editor

University of California, Irvine, Medical Center, Department of Obstetrics and Gynecology, Building 16, 101 City Dr. S., Orange, California 92668

Albert B. Gerbie, Associate Editor
710 North Fairbanks Court, Chicago, Illinois 60611

legends, and marked lightly on the back with the author's name. Authors should indicate on the manuscript the approximate position of tables and text figures.

Tables should be typed on separate sheets of paper, not in the text, with one table to a page. They should be numbered in sequence and each must be referred to at an appropriate point in the text. Captions of the tables should be brief, yet indicate clearly the purpose or content of each table. Rows and columns in the table should precisely define the nature of the data in each. Abbreviations in tables should be used as little as possible and if abbreviations are used they should be explained in a footnote to the table.

An abstract of 50 to 150 words, to be published as an introduction, should accompany each manuscript and should be typed on a separate sheet of paper.

A footnote should be included which gives the name and complete mailing address of the person to whom reprint requests and correspondence should be sent.

A Guide to Writing for the American Journal of Obstetrics and Gynecology may be obtained from the Publisher on request.

Illustrations. A reasonable number of halftone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the Editors for color plates, elaborate tables, or extra illustrations. Original drawings or graphs should be drawn with black India ink. Typewritten or freehand lettering is not acceptable. All lettering must be done professionally. Do not send original art work, x-ray films, or ECG tracings. Glossy print photographs are preferred, for good black and white contrast is essential. Illustrations will be returned only if requested by the author.

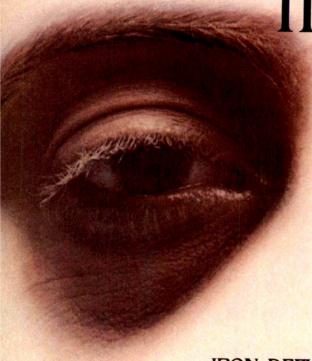
Announcements. Announcements of meetings must be received by Dr. Brewer at least 2½ months prior to the time of the meeting. Such announcements should concern major meetings and other significant activities. Announcements of symposia or seminars for which fees are charged are not published in the scientific pages of the JOURNAL but may be submitted for paid advertisements, if desired.

Letters to the Editors. A brief Letter to the Editors commenting upon some article which has appeared in the JOURNAL will be considered for publication. The writer of the original article will have an opportunity to reply to unfavorable comments. A brief case presentation of special interest in the form of a Letter to the Editors will also be considered for publication. All such letters should be sent to Dr. Zuspan.

**Books.** Books received will be listed in the JOURNAL. They should be sent to Dr. Gerbie.

**Reprints.** Reprints of articles must be ordered from the Publishers, The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141, who will send their schedule of prices. Individual reprints of an article must be obtained through the author.

# SOME PEOPLE CLAIM THEY WERE BORN





For patients with iron-deficiency anemia, Tabron provides 100 mg of elemental iron\* in a single tablet daily—enough to produce a clinically significant hemoglobin response.

General fatigue and lassitude are common presenting symptoms of the anemic patient. So when the patient complains about how difficult it has become to carry out normal sustained physical effort, it's logical to consider iron-deficiency anemia. And, what Tabron can do once the diagnosis is confirmed.

\*supplied as 304.2 mg of ferrous fumarate

### Each Tabron Filmseal® tablet represents:

rerrous lumarate (represents 100 mg of	
elemental iron)	304.2 mg
Vitamin C (ascorbic acid)	500 ma
Vitamin B <sub>1</sub> (thiamine mononitrate)	6 ma
Vitamin B <sub>2</sub> (riboflavin)	6 ma
Vitamin B <sub>6</sub> (pyridoxine hydrochloride)	5 mg
Vitamin B <sub>12</sub> (cyanocobalamin), crystalline	25 mcg
Folic acid*	1 mg
Nicotinamide (niacinamide)	30 mg
Calcium pantothenate	10 mg
Vitamin E (dl-alpha tocopheryl acetate), (30	ma) 30 IUt
Dioctyl sodium sulfosuccinate	50 mg
	-0 1119

\*CAUTION-Folic acid may obscure pernicious anemia; the peripheral blood picture may revert to normal while neurological manifestations remain progressive

†IU=International Units

CAUTION - Federal law prohibits dispensing without prescription.

# CORRECTS IRON-DEFICIENCY ANEMIA

**PARKE-DAVIS** 

Div of Warner-Lambert Co Morris Plains, NJ 07950 USA

© 1980 Warner Land

PD-JA-0284-1-P(3-80)

# American Journal of Obstetrics and Gynecology

Copyright © 1980 by The C. V. Mosby Company

Editors

John I. Brewer, Editor in Chief

710 North Fairbanks Court, Chicago, Illinois 60611

Frederick P. Zuspan, Editor

The Ohio State University, 410 W. 10th Ave., Columbus, Ohio 43210

E. J. Quilligan, Editor

University of California, Irvine, Medical Center, Department of Obstetrics and Gynecology, Building 16, 101 City Dr. S., Orange, California 92668

Albert B. Gerbie, Associate Editor

710 North Fairbanks Court, Chicago, Illinois 60611

Emeritus Editors

Howard C. Taylor, Ir.

200 E. 66th St., New York, New York 10021

Allan C. Barnes

111 W. 50th St., New York, New York 10020

Publisher

The C. V. Mosby Company

11830 Westline Industrial Drive

St. Louis, Missouri 63141

Entered at the Post Office at St. Louis, Mo., and additional mailing offices as Second-class matter.

#### **Business communications**

Business communications. All communications in regard to advertising, subscriptions, changes of address, etc., should be addressed to the Publisher, The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141.

1980 Annual subscription rates	U.S.A.	Foreign countries (surface mail) All regions	Region 1	Foreign countries (airmail)* Region 2	Region 3
Institutional†	\$52.50	\$72.50	\$101.45	\$132.65	\$163.85
Individual‡	\$35.50	\$55.50	\$ 84.45	\$115.65	\$146.85
Student, resident‡	\$28.40	\$48.40	\$ 77.35	\$108.55	\$139.75

Single copies are \$4.50 postpaid. Remittances should be made by check, draft, or post office or express money order, payable to this Journal.

\*Airmail breakdown—Domestic: First-class and Priority rates for the U.S. and possessions are available upon request. Region 1: Central America, islands, and mainland colonies of European countries in The Americas. Region 2: South America, Europe, Egypt, Africa (bordering the Mediterranean). Region 3: Asia, Australasia, Africa (other than Mediterranean),

Middle East, Far East, The Pacific, U.S.S.R. (and constituent Republics). †Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics; city, county, state, provincial, and national government bureaus and departments; and all commercial and private institutions and organizations.

‡Personal subscriptions and all student-rate subscriptions must be in the names of, billed to, and paid by individuals. All student-rate requests must indicate training status and name of institution.

Subscriptions may begin at any time

Second-class postage paid at St. Louis, Missouri, and additional mailing offices. Printed in the U.S.A. Copyright © 1980 by The C. V. Mosby Company.

Publication order. The semimonthly issues of this JOURNAL form three volumes per year; the index is in the last issue of the volume—in the April 15, August 15, and December 15 issues.

Change of address notice. Six weeks' notice is required to effect a change of address. Kindly give the exact name under which a subscription is entered, the name of this JOURNAL, and the full form of both old and new addresses, including the ZIP code number.

Advertisements. Forms close 1st of previous month for the 1st of month issue: 15th of preceding month for the 15th of month issue. Advertising rates and page sizes will be given on application. Neither the Editor(s) nor the publisher guarantee, warrant, or endorse any product or service advertised in this publication, nor do they guarantee any claim made by the manufacturer of such product or service.

Bound volumes. Bindery Corporation of America, 4440 West Roosevelt Road, Chicago, Illinois 60624, will quote prices for binding complete volumes in permanent buckram.

The appearance of a code at the bottom of the first page of an original article in this JOURNAL indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc., 21 Congress St., Salem, Mass. 01970, (617)744-3350, for copying beyond that permitted by Section 107 or 108 of the U. S. Copyright Law. This consent does not extend to other kinds of opying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale. For reprint quantities of 50 or more, please contact Publisher.

# For oc patients When the right move

Whether you're

MOVING DOWN FROM 80 mcg

You want to move your patient down from her high estrogen dose without compromising cycle control. Your best move may be to 50 mcg OVRAL, a balanced combination of norgestrel and ethinyl estradiol. A move down to OVRAL affords your patient strong support of the endometrium. And the incidence of common side effects is very low with 50 mcg OVRAL.\*

# OR UP FROM 35 mcg

Some women on sub-50
OC's suffer from continuing
breakthrough bleeding.
For the majority of
these women, a move to 50
mcg OVRAL offers a degree of
endometrial maintenance
which usually precludes intermenstrual bleeding. And
in most patients there's been
relative freedom from other
minor side effects.\*

\*Serious as well as minor adverse reactions have beer reported following the use of all oral contraceptives

# is to 50 mcg

# OR OVER FROM ANOTHER 50 mcg

Your patient breaks through on her 50 mcg pill, and you don't want to increase her dose. Why not move her to 50 mcg OVRAL? In clinical studies, breakthrough bleeding occurred in only 1% of total cycles, spotting in 1.5% and amenorrhea in 0.7%. And the incidences of other minor side effects, such as nausea and vomiting, headache and weight gain, were also very low.\*

Move to 50 mcg OVRAL. Distinguished by norgestrel.

Ovral

each tablet contains 0.5 mg norgestrel with 0.05 mg ethinyl estradiol, Wye

So often the right move to make

See important information on following page!

IN BRIEF:
Indications and Usage — OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

method of contraception.

Contraindications—OC's should not be used in women with
any of the following conditions: 1. Thrombophlebilis or thromboembolic
disorders. 2. A past history of deep-vein thrombophlebilis or
thromboembolic disorders. 3. Cerebal-vascular or coronary-artery
disease. 4. Known or suspected carcinoma of the breast. 5. Known
or suspected estrogen-dependent neoplasia. 6. Undiagnosed abnormal
genital bleeding. 7. Known or suspected pregnancy (see Warning
No. 5).

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke. The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infaction, hepatic adenoma, galibladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

Thromboembolic Disorders and Other Vascular Problems: An Intromobembolic cursoriers and urner vascular Propients: An increased risk of thromboembolic and thrombolic disease associated with use of OCs is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of Italal and nonitalal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident

CEREBROVASCULAR DISORDERS

CELEBROVASCULAR DISDRUERS in a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than

MYDCARDIAL INFARCTION (MI)

An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary-artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk of developing MI. regardless of whether the patient was an OC user or not. OCs, however, were found to be a clear additional risk factor. In terms of relative risk, if has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a talatl MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of talatl MI compared to users who do not smoke. Dut about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to RISK OF DOSE

In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboretrolling systems, or billist investigators concluded mat risk of thrombo-embolism, including coronary thrombosis, is directly related to dose of estrogen in OCs. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the LLS.

one struger may note the sole factor involved. This Indiang has been confirmed in the U.S. ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thrombomethod include combined risk of contraceptive method (e.g., thromboembolic and thrombolic disease in the case of OC's) plus risk
attributable to pregnancy or abortion in event of method (e.g., thromboembolic and thrombolic disease in the case of OC's) plus risk
attributable to pregnancy or abortion in event of method failure. This
latter risk varies with effectiveness of method. The study concluded that
mortality associated with all methods of birth control is low and below
that associated with philobirth, with the exception of OC's in women
over 40 who smoke. Lowest mortality is associated with condom or
diaphragm backed up by early abortion. Risk of thromboembolic and
thrombolic disease associated with OC's increases with age after about
30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and
especially cigarette smoking. Physician and patient should be alert to
earliest manifestations of thromboembolic and thrombolic disorders
(e.g., thrombophlebitis, pulmonary embolism, cerebrovascular
insufficiency, coronary occlusion, retinal thrombosis, and mesenteric
thrombosis, Should any of these occur or be suspected, the drug
stroid be discontinued immediately. A 4- to 6-fold increased risk
of patsurgery thromboembolic complications has been reported

Lisers.
If leashle, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

Coular Lesions: There have been reports of neuro-ocular lesions such

optic peuritis or retinal thrombosis associated with use of OC's Disconlinue OC's if there is unexplained, sudden or gradual, partial or comp fe loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular legions, and institute appropriate diagnostic and retinar-vascular therapeutic measures.

3. Carcinoma: Long-term continuous administration of either natural or

synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix: vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 2T cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported supposition increased risk of synthetic estrogen in certain animal species increases frequency of occurred in worlier with on ad used a sequential UC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OCs. Several studies have found no increase in breast cancer in women taking OCs or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OCs. found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

elect to use OC's.

4. Hepatic Tumors: Benign hepatic adenomas have been found to be associated with use of OC's. Che study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presention addominal rapin and federages; beforeal energy the property of the property women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatoeefular carcinoma have been reported in women on OCs. Relationship of these drugs to this type of malignancy is not known.

women on OCs. Relationship of these drugs to this type of malignancy is not known.

5. Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring. Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrio. It has been shown that remales exposed in utero to diethylstilbestrio. It has been shown that emales exposed in utero to diethylstilbestrio. It has been shown that or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1.000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's Furthermore. 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of imbreduction defects in rinafts exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy or attempted treatment of the trace and the process of the process of the order and the process of the process

of limb-reduction defects in infants exposed in utero to sex hormones (OCs, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births in the past, lemale sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after casing OCs. Embryos with these anomalies are virtually always aborted spontaneously Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OCs is of which with the commended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OCs. If the patient has not adhered to the prescribed schedule, the possibility of gregnancy should be considered at time of conlinuing OCs. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OCs should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the petential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OCs with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of propestogen-extreme prohipations to include the precise of the precise information is available on which to base this. The

although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy. 6. Galibladder Disease: Studies report increased risk of surgically confirmed galibladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years: use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months use. 7. Carbohydrate and Lipid Metabolic Effects: Decrease in glucose tolerance has been observed in a significant percentage of natients.

Carbonydrate and Lipid Metabolic Effects: Decrease in glucose tolerance has been observed in a significant percentage of patients on OCs. For this reason, prediabetic and diabetic patients should be carefully observed while on OCs. Increase in triglycerides and total phospholipids has been observed in patients on OCs; clinical significance of this inding remains to be defined.

8. Elevated Blood Pressure: Increase in blood pressure has been reported in patients on OCs. In some women, hypertension may occur within a few months of beginning OCs. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of possures. prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OCs. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. Headache: Onset or exacerbation of migraine or development of headache is now pattern which is required, precision or exacerbation of migraine or development.

9. Readactie: Oilse or exactigation of migraine or development headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of DCs and evaluation of the cause.
10. Bleeding Irregularities. Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing DCs. In breakthrough bleeding, as in all cases of irregular vaginal bleeding.

nonfunctional causes should be borne in mind. In undiagnosed nonfunctional causes should be borne in mind in undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy if pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a proderor to regard amenorrhea or proving women without regular cycles may have landency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these preexisting problems should be advised of this possibility and encouraged to use other methods. Postuse anovulation, possibly protonged, may also occur in women without possibly protonged.

use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. Ectopic Pregnancy: Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. Breast-Feeding: OCS given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OCs has been identified in the milk of mothers on OCs; effects, if any, on the breast-led child have not been determined. If feasible, defer OC's until infant has been weaped. has been weaned

Precautions—GENERAL

Trecations—GENERAL

A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests
As a general rule OC's should not be prescribed for longer than
1 year without another physical examination
2. Under influence of estrogen-progestogen preparations, preexisting

2. Under influence of estrogen-progestogen preparations, precisionly uterine leionymonata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed white on OC's should stop OC's and use an alternate method to try to determine whether the

stop OC's and use an alternate method to try to determine whether this symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patents with conditions which might be aggravated by fluid retention, such so convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of resurrence within an OC's. It inaution developes OC's.

increased risk of recurrence while on OC's. If jaundice develops, OC's

increased risk of recurrence write on too's in journal of execution increased risk of recurrence write on too's in journal of execution in should be discontinued. 6 Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution. 7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance

undetermined.
Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of foliate deficiency and incidence of foliate deficiency increases with increasing gestation; it is possible that if a woman becomes pregnant shortly after stopping OCs, she may have a greater chance of developing foliate deficiency and complications attributed to this deficiency

The pathologist should be advised of OC therapy when relevant specimens are submitted.

Certain endocrine- and liver-function tests and blood components.

10. Certain endocrine: and liver-function tests and blood components may be affected by estrogen-containing OCs:

a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X, decreased antifromobin 3; increased norepinephrine-induced platelel aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin update is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased

he elevated TBG, free T4 concentration is unallered d. Decreased pregnanediol excretion e. Reduced response to metyrapone test. Information for the Patient—See Patient Package Labeling. Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomilant use of rilampin. A similar association has been suggested with barbiturates, phenylbutazone, phenyloin sodium, and ampicillin. Carcinogenesis—See Warnings on carcinogenic potential of OC's. Pregnancy—Category X. See Contraindications. Warnings. Nursing Mothers—See Warnings on Carcinogenic potential of OC's. Pregnancy—Category X. See Contraindications. Warnings. Nursing Mothers—See Warnings. Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): htrombophieblis, pulmonary embolism, coronary thrombosis, cerebral hrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benigh hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's atthough additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., relinal thrombosis and optic neuritis. The following adverse reactions have been reported in patients on OC's. neuro-coular lesions, e.g., retinal thrombosis and optic neuritis. The following adverse reactions have been reported in patients on OCs and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, sopting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary intertility after discontinuance of treatment; edema; chloasma or melasma which may persist, breast changes; tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum, cholestatic jaundice; migraine; increase in size of uterine leiomyomata: possible diffinition in lactation when given immediately postpartum; cholestatic jaundice; migratine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis, change in corneal curvature (sleepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's.

and the association has been neither confirmed nor retuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystilis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema

nodosum, hemorrhagic eruption, vaginitis, porphyria **Acute Overdose**— Serious ill effects have not been reported following
acute ingestion of large doses of OCs by young children. Overdosage
may cause nausea, and withdrawal bleeding may occur in temales.

each tablet contains 0.5 mg norgestrel with 0.05 mg ethinyl estradiol. Wyeth Laboratories

COPYRIGHT (C) 1980, WYETH LABORATORIES. ALL RIGHTS RESERVED.

# American Journal of Obstetrics and Gynecology

volume 138 number 1

**SEPTEMBER 1, 1980** 

### **OBSTETRICS**

# Postural blood pressure differences in pregnancy

A prospective study of blood pressure differences between supine and left lateral position as measured by ultrasound

P. W. J. VAN DONGEN, M.D.\*

T. K. A. B. ESKES, M.D.

C. B. MARTIN, M.D.

M. A. VAN 'T HOF, Ph.D.

Nijmegen, The Netherlands

Differences in blood pressure between the supine and left lateral positions were studied in pregnant subjects under standardized conditions with an automated ultrasound device. Cross-sectional studies were performed in 125 nulliparous pregnant women after the twenty-eighth week of amenorrhea and in 42 nonpregnant controls. Arterial blood pressure in the left lateral position was lower than in the supine position. This difference was due largely to differences in hydrostatic pressure. Large errors in measurement and regression to the mean contributed to a wide spread in measured values. Neither hypertension nor pregnancy alone gave an enhanced postural difference in blood pressure. Hypertension in pregnancy was associated with a significantly larger positional change in diastolic blood pressure (D) than in systolic blood pressure (S). This study pleads for a standardized procedure for the measurement of blood pressure in gravidas in the supine position, for the detection of peripheral vasoconstriction in the supine position, and to compare clinical blood pressure studies in different institutions. (Am. J. Obster. Gynecol. 138:1, 1980.)

POSITIONAL changes in arterial blood pressure during pregnancy in the human being became interesting

From the Departments of Obstetrics and Gynecology, Sint Raaboud Ziekenhuis and Statistical Consultation, Catholic University.

Presented in part at the Annual Meeting of the Society for Gynecologic Investigation, San Diego, California, March 21-23, 1979, and the First Congress of the International Society for the Study of Hypertension in Pregnancy, Dublin, Ireland, September 27-29, 1978.

Received for publication September 24, 1979.

for obstetricians because of the "supine hypotensive syndrome" and, more recently, because of the de-

Revised March 6, 1980.

Accepted March 27, 1980.

Reprint requests: T. K. A. B. Eskes, M.D., Professor and Chairman, Department of Obstetrics and Gynecology, St. Radboud Hospital, Catholic University, Nijmegen, The Netherlands.

\*Present address: Muhimbili Medical Centre, P. O. Box 20500, Dar es Salaam, Tanzania.

0002-9378/80/170001+05\$00.50/0 © 1980 The C. V. Mosby Co.

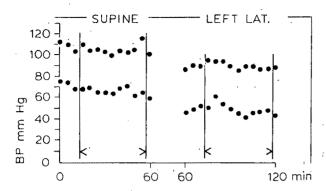


Fig. 1. Automated ultrasound arterial blood pressure measurement in a pregnant subject. Values between vertical rules were used for statistical analysis.

scription of the "roll over test" for predicting the development of pregnancy-induced hypertension (PIH). Arterial blood pressure is usually highest when the patient is seated, intermediate when she is supine, and lowest when she is lying on the left side. To minimize the large observer errors inherent in the auscultatory measurement of blood pressure, arterial blood pressure in this investigation was recorded repeatedly with an automated ultrasound device, with the patient under stable resting conditions.

### Material and methods

A prospective study of arterial blood pressure was carried out. Arterial blood pressure was measured in the right upper arm with an automated ultrasound device (Arteriosonde, Roche Medical Electronics Division, Hoffmann-LaRoche, Inc., Cranbury, New Jersey). The Arteriosonde was connected to a matching analog recorder from the same firm. The maximal cuff-inflation pressure was set to a point 30 mm Hg higher than the auscultatory systolic pressure. The deflation rate was set at three heartbeats per 10 mm Hg. The ultrasound transducer was placed in its holder in the cuff and covered with a water-soluble ultrasound transmission gel (Aquasonic, Parker Laboratories, Inc., Orange, New York). The length of the cuff was 42 cm; the size of the air bag was 12 by 23 cm. Measurements were made at 5-minute intervals during 120 minutes with the patients in the supine and left lateral positions. A possible effect of the sequence of positions employed was investigated by alternating the starting position and sequence of positions in a subgroup of 10 patients. The first three values, as well as the last value, in each position were disregarded. Nine values were used for statistical evaluation (Fig. 1). Duplicate blood pressure measurement error (e) was calculated according to the formula

$$e = \sqrt{\sum d_1^2/2} n$$

in which  $d_1$  = the difference between both measurements of the  $i^{th}$  pair, and n = the number of paired observations. Student's one-sample t test was used when the mean value of a series of observations had to be tested against zero. Relationships between variables were studied by analysis of variance, correlation coefficients (Pearson's product moment method), and multiple regression analysis.

A total of 125 nulliparous pregnant women participated in the study. They were admitted in the second half of pregnancy, mostly because of hypertension and/or suspected fetal growth retardation, and were studied under conditions of bed rest and standardized sodium intake (i.e., less than 20 millimoles per 24 hours). This group of pregnant subjects could be divided into three subgroups. (1) Eighty-four pregnant nulliparous women had pregnancy-induced hypertension (PIH). This condition was defined as a casual diastolic blood pressure of more than 90 mm Hg auscultatory in the supine position any time after 28 weeks of gestation without preexisting hypertension. (2) Twenty-two subjects with pre-existing hypertension who demonstrated aggravation of the hypertension or other evidence of superimposed toxemia. (3) Nineteen pregnant nulliparous subjects who remained normotensive. Excluded from the study were individuals who had a menstrual age of less than 28 weeks, twin pregnancy, or diabetes mellitus, were taking medication other than iron supplements, or had polyhydramnios or "supine hypotensive syndrome" (n = 2).

#### Results

Uniformly, a lower blood pressure was measured in the left lateral than in the supine position (Fig. 1). To gain insight into this difference, we carried out a control of measurement methods.

**Sequence of postures.** In 10 pregnant patients the sequence of measurements was alternated between supine, left lateral, supine (Group A, n = 5) and left lateral, supine, left lateral (Group B, n = 5). The postural blood pressure differences were essentially the same in the two groups regardless of the sequence of postures (Table I).

Effective measurement errors. Resting blood pressures were recorded in eight nonpregnant milliparous controls and repeated after 2 months under the same conditions. The duplicate errors for the postural blood pressure differences were: for the systolic value ( $\Delta S$ ), 5.5 mm Hg; for the diastolic value ( $\Delta D$ ), 5.5 mm Hg; for the mean arterial pressure ( $\Delta MAP$ ), 4.8 mm Hg; and for the pulse pressure value ( $\Delta P$ ), 4.8 mm Hg.

Hydrostatic pressure. In order to evaluate the role of hydrostatic pressure differences, the distance be-

Table I. Postural blood pressure differences between subjects with sequence of postures: Supine, left lateral, supine (Group A; n = 5); left lateral, supine, left lateral (Group B; n = 5)

	$\Delta I = \Delta(S \to L)$	$\Delta 2 = \Delta(L \to S)$	$\Delta I - \Delta 2$	t value*	Significance
A Systolic	14.0 (3.0)	13.9 (3.9)	0.1 (6.1)	0.03	NS
B Systolic	23.8 (2.6)	18.4 (7.1)	5.4 (7.7)	1.40	. NS
A Diastolic	20.0 (4.1)	13.0 (1.7)	7.0 (5.4)	2.60	NS
B Diastolic	19.0 (8.5)	19.7 (6.6)	0.7 (12.8)	0.11	NS

Presented are the mean values, with the standard deviations in parentheses.  $\Delta I = Postural$  differences with supine as starting position.  $\Delta 2$  = Postural differences with left lateral as starting position.  $\Delta 1 - \Delta 2$  = Difference of the postural differences.

Table II. Distances (cm) between atrium and right upper arm in control subjects

Males: 17	Nonpregnant females: 17
15.5	13.9*
1.6	_ 1,9
14-20	12-20
	15.5 1.6

 $p < 0 \sim 05$ .

tween the xiphoid process and the right atrium was measured in 17 male and 17 female controls. The mean hydrostatic pressure component could be calculated to be 15.5 cm or 11.7 mm Hg for the males and 13.9 cm or 10.5 mm Hg for the females (Table II). The observed postural blood pressure differences were 1 to 8 mm Hg greater than these calculated values.

Basal blood pressure versus postural blood pressure differences. The correlation coefficients for the differences between the diastolic blood pressures and positional diastolic blood pressure differences (\D) were positive for the supine position (Table III) and negative for the left lateral position. In three instances the correlations reached statistical significance; however, the signs of these significant correlations were different (Table III). The positional blood pressure differences were then compared with an "average" blood pressure, calculated as the mean of the supine and left lateral readings for each subject. No significant correlations were found.

Postural blood pressure differences in normotensive and hypertensive gravidas. The mean postural differences for systolic, diastolic, and mean arterial blood pressure and pulse pressures for normotensive pregnant patients were not significantly different from those observed in the nonpregnant control groups. The postural differences in systolic, diastolic, and mean arterial blood pressures did not differ significantly between the three subgroups of pregnant subjects (Table IV) (one-way analysis of variance). However, in both of the hypertensive groups the postural differences in diastolic blood pressures were significantly greater than

Table III. Correlation coefficients (Pearson) between diastolic pressure and its postural differences ( $\Delta$ )

, ,				
Groups	V.	Supine BP vs. \(\DD\)	Left lateral BP vs. ΔD	Average BP vs. ΔD
Controls, male	17	0.33	-0.39	-0.03
Controls, nulliparas	25	0.22	-0.24	-0.01
No hypertension	19	0.15	-0.57*	-0.26
Pre-existing hyper- tension	22	0.10	$-0.48\dagger$	-0.22
Pregnancy-induced hypertension	84	0.22†	-0.33	-0.06

<sup>\*</sup>p < 0.01.

the corresponding postural differences in systolic blood pressure, since both hypertensive groups showed significant negative mean values for the postural differences in pulse pressure ( $\Delta P$ ). This was not demonstrated in the normotensive gravidas. Additionally, the ΔPs were significantly more negative in the two hypertensive groups than in the normotensive group (one-way analysis of variance, p = 0.05).

#### Comment

It should be apparent to the thoughtful physician that the indirect measurement of blood pressure is subject to many inaccuracies, including those arising from the equipment, as well as errors and biases on the part of the observer/operator. The sources of these inaccuracies have been reviewed by Rose and associates8 and by Kirkendall and co-workers.9

In the present study, we tried to minimize observer problems by using an automated Doppler-ultrasound apparatus to measure and record blood pressure. Random measurement errors were minimized by averaging nine values obtained at 5-minute intervals. The measurements were carried out under stable, resting conditions, and the values obtained immediately before and after the subject was disturbed for position changes were discarded. In spite of these precautions, duplicate measurement errors in the range of 5 mm

<sup>\*</sup>t value according to Student's one-sample t test for  $\Delta 1 - \Delta 2 = 0$ ; t value depends on 4 degrees of freedom.

<sup>\*</sup>t = 2.66.

<sup>†</sup>p < 0.05.

**Table IV.** Postural differences of blood pressures ( $\Delta$ ) in nonpregnant controls and normotensive and hypertensive gravidas

	Nonpregnant $(n = 25)$	Pregnant, normotensive $(n = 19)$	Pregnant, pre-existing hypertension $(n = 22)$	Pregnant, pregnancy- induced hypertension $(n = 84)$	Significance*
ΔS	11.3 (4.9)	14.0 (4.3)	11.9 (6.8)	12.5 (6.2)	NS
$\Delta D$	12.4 (4.5)	15.9 (5.3)	18.6 (5.7)	17.6 (5.5)	NS
$\Delta M$	11.8 (3.9)	14.4 (4.0)	14.0 (6.0)	14.1 (5.1)	NS
ΔΡ	-1.1(5.3)	-1.9(5.8)	-6.7(6.1)	-5.1(6.6)	p = 0.05
	p > 0.1†	+1.0 < q	$p < 0.01 \uparrow$	p < 0.017	

Presented are the mean values (mm Hg), with standard deviations in parentheses.  $\Delta S = Systolic blood pressure$ ;  $\Delta D = diastolic blood pressure$ ;  $\Delta M = mean arterial pressure$ ;  $\Delta P = pulse pressure$ .

\*One-way analysis of variance. Differences between the three pregnant subject groups.

†One-sample Student's t test:  $\Delta P$  tested against zero.

Hg were found. Moreover, inspection of Fig. 1 demonstrates that differences between maximum and minimum blood pressures recorded during a 45-minute period, at rest, could exceed 10 mm Hg. The degree to which these differences in measured blood 'pressure represent actual differences (due, for example, to ultradian or sporadic blood pressure variation) or measurement error was not established by direct (intraarterial) measurement techniques; however, these observations suggest that caution is advisable in attaching significance to even moderate changes in blood pressure in individual subjects. Although the averaging of data from many subjects may be expected to reduce the effect of random measurement errors when groups of subjects are compared, this is not always the case, as demonstrated by the spurious but statistically significant correlations between resting blood pressure and positional changes in some instances. The significant positive correlation coefficient between the resting blood pressure in the supine position and the postural blood pressure differences in the women with PIH might suggest that hypertension is related to greater postural blood pressure differences.

Since the left lateral blood pressure was highly correlated with the blood pressure in the supine position, one might also expect to see the same tendency for the left lateral blood pressure values. However, the correlation coefficients in the left lateral position were negative and were statistically significant in two of the five subject groups. The explanation for this paradox can be found in the relatively large measurement errors.

Since the resting blood pressure in the supine position was uniformly higher than that in the left lateral position, an overestimate of blood pressure in the supine position would also tend to produce a falsely great positional change and the reverse. Conversely, an underestimate in the left lateral position would increase the apparent positional change, whereas a positive error would reduce it. Thus, the apparent correla-

tions between resting blood pressure and positional change represented, on further analysis, the phenomenon of correlation with initial value or, in more general terms, "regression to the mean." <sup>10</sup>

When, as is the usual practice, the blood pressure cuff is applied around the right arm, in the left lateral position the heart is lower than the site of blood pressure measurement, whereas in the supine position the heart and the site of the blood pressure measurement lie in about the same horizontal plane. Thus, the measured blood pressure values in the left lateral position will be lower than those in the supine position because of the hydrostatic pressure differences. Measurements in nonpregnant women indicate that, on the average, a 10.5 mm Hg positional blood pressure difference would result from this hydrostatic pressure gradient. In pregnant subjects the hydrostatic contribution may be slightly great because of changes in the configuration of the rib case.

Although hydrostatic pressure could be calculated to account for the greatest part of the observed positional differences in blood pressure, our findings do not exclude a contribution from changes in vascular resistance and/or cardiac output. The observed average positional differences in systolic, diastolic, and mean blood pressure were slightly greater in all subject groups than the expected hydrostatic pressure difference. This tendency was greatest for  $\Delta D$  in the two categories of hypertensive gravidas. Furthermore, the change in hydrostatic pressure should affect systolic and diastolic pressures equally. However, in both groups of hypertensive subjects, the values for  $\Delta D$  exceeded those for  $\Delta S$  (Table IV). This finding may have reflected the combined effects of diminished blood volume in hypertensive gravidas as compared to normotensive gravidas<sup>11</sup> and vena caval compression in reducing venous return and cardiac filling. The resulting hemodynamic alterations could have served additionally as a stimulus to increased peripheral vascular tone and, thus, to increased diastolic blood pressure in the supine position. Therefore, the finding of a greater average  $\Delta D$  than  $\Delta S$  in the hypertensive gravidas is compatible with the concept, prevailing in the literature, of enhanced vascular reactivity in hypertensive subjects.

Despite this possible indication of enhanced vascular reactivity in hypertensive gravidas, the differences in average  $\Delta D$ ,  $\Delta S$ , and  $\Delta M$  were insignificant between the normotensive and hypertensive subject groups. These findings, together with the variations (up to 10 mm Hg) in measured blood pressure during the 30-minute stable test periods, estimate of duplicate measurement errors (mean, 5 mm Hg), and hydrostatic pressure effect (10.5 mm Hg), demonstrate that caution should be exercised in attributing significance to positional blood pressure differences measured by clinical methods in individual gravidas.

#### REFERENCES

- 1. Hanssen, R.: Ohnmacht und Schwangerschaft (Fainting and pregnancy), Klin. Wochenschr. 11:241, 1942.
- Gant, N. F., Chaud, S., Worley, R. J., Whalley, P. Crosby, U. D., and MacDonald, P. C.: A clinical test useful for predicting the development of acute hypertension in pregnancy, Am. J. Obstet. Gynecol. 120:1, 1974. Schwarz, R.: Das Verhalten des Kreislaufs in der norma-
- len Schwangerschaft, Arch. Gynaekol. 199:663, 1964.
- 4. Trower, R., and Walters, W. A. W.: Brachial artery blood pressure in the lateral recumbent position during preg-
- nancy, Aust. N. Z. J. Obstet. Gynaecol. 8:146, 1968. 5. Eskes, T. K. A. B., Weyer, A., Kramer, N., and Van Elteren, Ph.: Arterial blood pressure and posture during pregnancy, Eur. J. Obstet. Gynaecol. Reprod. Biol. 413:87, 1974.
- 6. Van Dongen, P. W. J.: Postural blood pressure differences in pregnancy, Ph.D. Thesis, University of Nijmegen, The Netherlands, 1979.

- 7. Gant, N. F., Daley, G. L., Chaud, S., Whalley, P. J., and MacDonald, P. C.: A study of angiotensin II pressor response throughout primigravid pregnancy, J. Clin. Invest. 52:2682, 1973.
- 3. Rose, G. A., Holland, W. W., and Crowley, E. A.: A sphygmomanometer for epidemiologists, Lancet 1:296,
- 9. Kirkendall, W. M., Burton, A. C., Epstein, F. H., and Freis, E. D.: Recommendations for human blood pressure determination by sphygmomanometers, Circulation **36:**980, 1967.
- 10. Van't Hof, M. A.: Some statistical and methodological aspects in the study of growth and development, Thesis, Catholic University, Nijmegen, 1977.
- 11. Arias, F.: Expansion of intravascular volume and fetal outcome in patients with chronic hypertension and pregnancy, Am. J. Obstet. Gynecol. 123:610, 1975.

# Hemodynamic observations in evacuation of molar pregnancy

DAVID B. COTTON, M.D.

STEVEN G. BERNSTEIN, M.D.

JOHN A. READ, M.D., LIEUTENANT COLONEL, MC, USA
THOMAS J. BENEDETTI, M.D.\*

GERRIT D'ABLAING, M.D.

FRANK C. MILLER, M.D.

C. PAUL MORROW, M.D.

With the technical assistance of
GARY M. FLYNN

Los Angeles, California

The high incidence of pulmonary complications following evacuation of molar gestation at 16 weeks' size or greater (27%) prompted us to institute hemodynamic monitoring in seven of these patients in an effort to determine etiologies and possible modes of therapy for this potentially life-threatening complication. Our data indicate that following suction curettage with general anesthesia there appears to be impairment of ventricular performance of a transient nature as manifested by increases in central venous pressure, mean pulmonary artery pressure, and pulmonary capillary wedge pressure, despite a slight elevation in cardiac index and a decrease in systemic vascular resistance. The possible role of general anesthesia in the development of these changes, as well as the role of the colloid osmotic pressure to wedge gradient in the development of pulmonary complications, is discussed. (AM. J. OBSTET. GYNECOL. 138:6, 1980.)

A RECENT REVIEW at our institution of pulmonary complications following evacuation of molar pregnancy documented a 27% incidence of acute respiratory insufficiency in the early postevacuation period among patients with a uterus of 16 weeks' size or greater.<sup>1</sup>

From the Department of Obstetrics and Gynecology, University of Southern California School of Medicine, and Women's Hospital, Los Angeles County-University of Southern California Medical Center.

Supported in part by Fellowship Training Grant No. HD07086-04 from the National Institutes of Health, Trophoblastic Disease Program No. 2, R18, CA 20749-04, and Wright Foundation Grant No. 55.

Presented at the Twenty-seventh Annual Meeting of the Society for Gynecologic Investigation, Denver, Colorado, March 19-22, 1980.

Received for publication January 28, 1980.

Accepted March 27, 1980.

Reprint requests: David B. Cotton, M.D., Alta Bates Hospital, 3001 Ashby St., Berkeley, California 94705.

\*Current address: Department of Obstetrics and Gynecology, Division of Perinatal Medicine, University of Washington, Seattle, Washington. Possible etiologies suggested for the development of pulmonary complications after evacuation include trophoblastic embolization, 1, 2 high output failure secondary to thyrotoxicosis, 3 and iatrogenic fluid overload. 1 Because of the rather marked incidence of pulmonary complications in patients with a uterus of 16 weeks' size or greater, we elected to institute hemodynamic monitoring in these patients in an effort to determine possible etiologies and ultimately preventative measures that could be taken to avoid this potentially lifethreatening situation.

#### Material and methods

We evaluated seven patients with molar gestations of 16 weeks' size or greater. The mean maternal age was 20.4 (range 16 to 24) years with the mean gravidity and parity being 2 (range 1 to 5) and 0.3 (range 0 to 1), respectively.

All patients were in a state of relative clinical stability without evidence of respiratory embarrassment or excessive vaginal bleeding prior to evaluation. Thiopental, nitrous oxide, and oxygen with narcotic supplementation (most commonly fentanyl) were used for

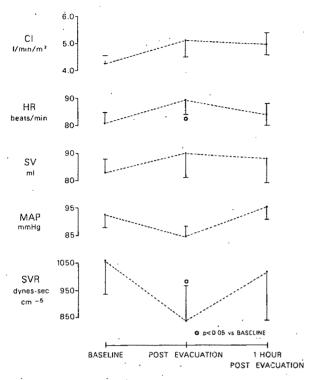


Fig. 1. Changes in CI, HR, SV, MAP, and SVR are illustrated. Hemodynamic variables were determined prior to suction curettage with general anesthesia, immediately following evacuation and extubation, and I hour after extubation. Values are expressed as mean  $\pm$  SEM. Stars denote p < 0.05 when baseline values are compared to postextubation values.

balanced general anesthesia in all cases. Premedication usually consisted of meperidine, promethazine or hydroxyzine, and atropine.

Hemodynamic measurements. After written informed consent was obtained, catheterization of the right side of the heart, with a triple-lumen, flowdirected catheter (Swan-Ganz, Edwards Laboratories), and arterial cannulation of the radial artery were performed. Measurements were made with the zero reference level at the midaxillary line with the patient supine. Systemic and mean pulmonary arterial pressures were determined by electronic filtration. Thermodilution cardiac outputs were determined by a bedside cardiac output computer (Edwards Laboratories) with the use of iced injectate. Cardiac output measurements were made in duplicate unless there was a greater than 10% variation; then measurements were done in triplicate. Heart rates were derived from an electronic cardiotachometer.

The following hemodynamic variables were determined prior to induction of anesthesia, immediately following extubation, and 1 hour after extubation: (1) mean arterial pressure (MAP), (2) heart rate (HR), (3) central venous pressure (CVP), (4) mean pulmonary

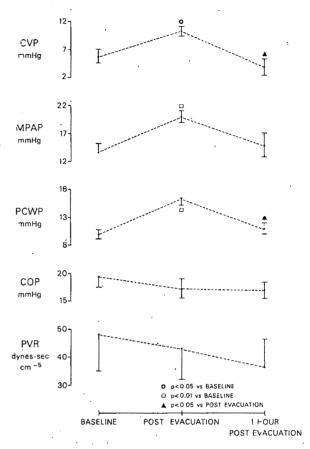


Fig. 2. Changes in CVP, MPAP, PCWP, colloid osmotic pressure (COP), and PVR are illustrated. Hemodynamic variables were determined prior to suction curettage with general anesthesia, immediately following evacuation and extubation, and 1 hour after extubation. Values are expressed as mean ± SEM. Stars denote p < 0.05, and squares denote p < 0.01when baseline values are compared to postextubation values. Triangles denote p < 0.05 when postextubation values are compared to 1-hour values.

artery pressure (MPAP), (5) pulmonary capillary wedge pressure (PCWP), and (6) cardiac output (CO). Derived hemodynamic variables were calculated as follows:

$$MAP = \frac{\text{systolic pressure} + 2 \times \text{diastolic pressure (mm Hg)}}{3}.$$

$$Cardiac index (CI) = \frac{CO \text{ (L/min/sq m)}}{\text{body surface area}}.$$

$$Systemic vascular resistance (SVR) = \frac{(MAP - CVP) 80 \text{ (dynes-sec cm}^{-5})}{CO}$$

Pulmonary vascular resistance (PVR) =

(MPAP - PCWP) 80 (dynes-sec cm

Plasma and blood volume studies. Colloid osmotic pressures were determined prior to anesthesia, immediately following extubation, and 1 hour after extuba-

Table I. Blood volume measurements, fluid requirements, and uterine size\*

	R. P.†	R. G.	L. M.	A. G.†	P. J.	L. T.‡
Plasma volume per kg	2,586 58	2,703 46	2,000 35	2,703 46	1,460	2,800
Red cell volume per kg	1,251	1,264	1,102	1,199	<b>29</b> 769	42 1,132
Total blood volume per kg	28 3,837	23 3,967	19 3.102	20 3,902	15 2,229	17 3.932
. 0	86	72	55	66	44	58
Crystalloids infused at procedure Estimated uterine size in weeks' gestation	1,530 21	1,200 16	1,425 16	1,930 18	1,050 20	$\begin{array}{c} 700 \\ 22 \end{array}$

<sup>\*</sup>Specimens for blood volumes of Patient L. A. were lost.

tion (Instruments Laboratories, Weil Oncometer).

A 5 ml tube containing ethylenediaminetetra-acetic acid was used to collect a pulmonary artery sample during the middle of the evacuation procedure. This sample was centrifuged as soon as possible; the buffy coat was aspirated, Wright stained, and microscopically examined for evidence of trophoblastic embolization.

Plasma volumes were determined with Evans blue dye (T-1824). A peripheral vein was punctured and 7 ml of blood was withdrawn for the baseline dye free sample and microhematocrit determination. Following this, 2 ml (10 mg/100 ml) of Evans blue dye was injected and blood for plasma samples and microhematocrit determination was drawn at 15, 25, and 35 minutes from a vein other than that injected. All samples were collected in siliconized, preheparinized test tubes. Blood samples were centrifuged at 2,500 rpm for 30 minutes and the plasma was removed. The base sample was used to zero the spectrophotometer (Bausch and Lomb Spectronic 100 set at wavelength 620 mu) and the 15-, 25-, and 35-minute samples were mated for optical density readings. These points were then extrapolated to obtain the calculated time zero optical density. The concentration of dye at time zero was then derived from a stock solution standard curve. Blood volume values were calculated by the following formulas:

Plasma volume =

concentration of Evans blue dye injected concentration of calculated optical density at time zero

Total blood volume = 
$$\frac{\text{plasma volume}}{1 - (0.96^*) \times \text{hematocrit}}$$

Statistical analysis. Statistical analysis by paired Student's t test was performed to detect differences in mean responses from baseline values prior to anesthesia and suction curettage and from those values ob-

\*The correction factor for trapped plasma is 0.96.

tained immediately after extubation and 1 hour after extubation. The Mann-Whitney U test was used to compare our blood volume values with those previously reported.<sup>4</sup>

#### Results

Figs. 1 and 2 illustrate baseline hemodynamic values and the changes that occurred immediately following suction curettage with general anesthesia and values observed 1 hour following the procedure. CI rose from 4.26 to 5.11 L/min/sq m and returned to 4.98 L/min/sq m by 1 hour. HR increased from 81 to 89 bpm and returned to 84 bpm by 1 hour. Stroke volume values at baseline, after evacuation, and 1 hour after evacuation were 83, 90, and 88 ml, respectively. The initial MAP of 92.6 mm Hg decreased to 84.4 mm Hg after evacuation and returned to 95.4 mm Hg by 1 hour. SVR decreased from 1 baseline value of 1,060 to 839 dynes-sec cm<sup>-5</sup> and returned to 1,015 dynes-sec cm<sup>-5</sup> by I hour. CVP rose from a baseline value of 5.8 to 10.3 mm Hg after evacuation and returned to 3.9 mm Hg by 1 hour. MPAP increased from 13.7 to 20.0 mm Hg after evacuation and decreased to 14.9 mm Hg by 1 hour. PCWP showed a similar trend with a rise from baseline values of 10.0 to 16.4 mm Hg after evacuation, decreasing to 11.0 mm Hg by 1 hour. PVR values at baseline, after evacuation, and 1 hour after evacuation were 48, 43, and 36 dynes-sec cm<sup>-5</sup>, respectively. Colloid osmotic pressures measured at baseline, after evacuation, and I hour after evacuation were 19.4, 17.2, and 16.9 mm Hg, respectively.

CI, stroke volume, MAP, and PVR distrot change significantly throughout the study. HR was significantly elevated from baseline (p < 0.05) immediately after evacuation with no significant differences between baseline and 1-hour values. CVP (p < 0.05), MPAP (p < 0.01), and PCWP (p < 0.01) were significantly elevated immediately after evacuation when compared to baseline values. There were no significant differ-

<sup>†</sup>Elevated thyroid function.

<sup>‡</sup>Clinically toxemic.

ences between baseline and 1-hour postevacuation values in any of the hemodynamic variables measured.

Colloid osmotic pressures showed a trend toward decreasing values that was not statistically significant.

None of the pulmonary artery samples collected for evidence of trophoblastic deportation revealed any trophoblastic cells by the method employed.

Blood volumes measured prior to suction curettage are illustrated in Table I. The mean plasma volume was 2,375 ± 222 ml (SEM). Mean red blood cell volume was  $1,120 \pm 76$  ml. Mean total blood volume was  $3.495 \pm 292$  ml.

The mean volume of crystalloids infused at anesthesia was  $1.306 \pm 387$  ml (SEM) with individual values shown in Table I. Uterine size ranged from 16 to 22 weeks' size. No significant clinical correlations could be obtained between any of the hemodynamic variables measured and uterine size, elevated thyroid function, or the presence of toxemia.

Only one patient in this study (L. T.) developed respiratory compromise, as evidenced by roentgenographic pulmonary vascular redistribution with fluid in the fissure of the right middle lobe and progressive oliguria. This patient also subsequently had a hysterectomy for hemorrhage, and an invasive mole was diagnosed. All other patients were free of any complications associated with molar pregnancy.

#### Comment

Our data indicate that following suction curettage with general anesthesia there appears to be impairment of ventricular performance of a transient nature. The evidence for this is suggested by the increases in CVP, MPAP, and PCWP that occurred despite a slight elevation in CI and a decrease in SVR. The decrease in SVR most likely results from peripheral vasodilation which, in turn, causes the significant elevation of HR seen immediately after evacuation and termination of anesthesia.

We speculate that the changes observed could be attributable to the effects of general anesthesia. Previous investigators have demonstrated a steady and apparently direct depression of myocardial function with nitrous oxide breathing, as evidenced by increases in CVP and left ventricular end diastolic pressure, as well as systemic vascular resistance.5, 6 Other studies of the combined effects of fentanyl and nitrous oxide in cardiac patients showed significant decreases in HR, MAP, and CI with no changes in SVR.7 Desmonts and associates,8 in a study of patients recovering from narcoticnitrous oxide anesthesia, demonstrated a significant increase in HR, MAP, CI, and left ventricular stroke work index with a significant decrease in systemic vascular resistance during the recovery period.

The changes observed could occur from a sudden increase in intravascular volume but, as can be seen from Table I, the amount of fluids received did not exceed 2,000 ml in any patient. However, the combination of hemodilution, as evidenced by a decreasing trend in colloid osmotic pressure; and an increasing PCWP do suggest a possible mechanism for pulmonary complications following molar evacuation. Patient L. T., the only patient in this series to develop pulmonary complications, had a colloid osmotic pressure to wedge gradient of -3 mm Hg. DaLuz and associates9 have reported the occurrence of pulmonary edema when the colloid osmotic pressure to wedge gradient is less than +4 mm Hg.

In the patients in this study the increase in MPAP and PCWP together with a normal PVR suggests an absence of significant trophoblastic embolization. This was supported by the lack of identifiable trophoblastic cells in the pulmonary artery samples collected during evacuation.

Blood volume measurements obtained in this study were in the normal nonpregnant range. 10-12 The plasma volumes were low for reported values at 20 weeks' gestation,13, 14 and the red cell volumes were somewhat low even for the nonpregnant state. We compared our values with those of a previous study and could demonstrate no statistically significant differences.4 In our study, hypervolemia was absent and, in fact, a state of relative hypovolemia for pregnancy was present.

In summary, our findings suggest that during molar evacuation with general anesthesia there is transient impairment of myocardial performance. Excessive crystalloid administration superimposed on a relatively hypovolemic state leading to low colloid osmotic pressures at a time when myocardial performance is not optimal may contribute to the development of pulmonary complications. Further investigation into alternative modes of anesthesia with molar evacuation needs to be undertaken.

### REFERENCES

1. Twiggs, L. B., Morrow, C. P., and Schlaerth, J. B.: Acute pulmonary complications of molar pregnancy, Am. J. OBSTET. GYNÉCOL. 135:189, 1979.

2. Llewellyn-Jones, D.: Management of benign trophoblastic tumors, Am. J. Obstet. Gynecol. 99:589, 1967.

Higgins, H. P., Herschmann, J. M., Kenimer, J. G., Patillo, R., Bayley, T. A., and Walfish, P.: The thy-

- rotoxicosis of hydatidiform mole, Ann Intern. Med. 83:307, 1975.
- 4. Pritchard, J. A.: Blood volume changes in pregnancy and the puerperium. IV. Anemia associated with hydatidiform mole, Am. J. Obstet. Gynecol. 91:621, 1965.
- 5. Eisele, J. H., and Smith, N. T.: Cardiovascular effects of 40 percent nitrous oxide in man, Anesth. Analg. (Cleve.) **51**:956, 1972.
- 6. Eisele, J. H., Reitan, J. A., Massumi, R. A., Zelis, R. F., and Miller, R. R.: Myocardial performance and N2O analgesia in coronary artery disease, Anesthesiology 44:16, 1976.
- 7. Stoelting, R. K., Gibbs, P. S., Creasser, C. W., and Peterson, C.: Hemodynamic and ventilatory responses to fentanyl, fentanyl-droperidol, and nitrous oxide in patients with acquired valvular heart disease, Anesthesiology **42:**319, 1975.
- 8. Desmonts, J. M., Bohm, G., and Couderc, E.: Hemodynamic responses to low doses of naloxone after narcoticnitrous oxide anesthesia, Anesthesiology 49:12, 1978.

- 9. DaLuz, P., Shubin, H., Weil, M. H., Jacobson, E., and Stein, L.: Pulmonary edema related to changes in colloid osmotic and pulmonary artery wedge pressure after acute myocardial infarction, Circulation 51:350, 1975.
- 10. Gibson, J. G., and Evans, W. A.: Clinical studies of the blood volume, J. Clin. Invest. 16:317, 1937.
- 11. Hurley, P. J.: Red cell and plasma volume in normal adults, J. Nucl. Med. 16:46, 1975.
- 12. Nadler, S. B., Hidalgo, J. U., and Bloch, T.: Prediction of blood volume in normal human adults, Surgery 51:224, 1962.
- 13. Chesley, L. C.: Plasma and red cell volumes during preg-
- nancy, Am. J. Obstet. Gynecol. 112:440, 1972.

  14. Hytten, F. E., and Leitch, I.: The volume and composition of the blood, in Hytten, F. E., and Leitch, I., editors: The Physiology of Human Pregnancy, ed. 2, Oxford, 1971, Blackwell Scientific Publications, p. 26.

## Acceptance of amniocentesis by low-income patients in an urban hospital

JANET P. MARION, M.S.
GULZAR KASSAM, M.D.
PAUL M. FERNHOFF, M.D.
KARLENE E. BRANTLEY, M.N.
LINDA CARROLL, M.N.
JUNE ZACHARIAS, M.N.
LUELLA KLEIN, M.D.
JEAN H. PRIEST, M.D.
LOUIS J. ELSAS II, M.D.
Atlanta, Georgia

A study was made of increased accessibility of genetic services to low-income obstetric patients in Atlanta, Georgia. The proportion of black patients averaged 83%. Of 522 patients counseled from August, 1976, through 1978, 157 were offered amniocentesis, and 95 (51%) elected the procedure. For most of the patients (120, or 76%) who were eligible for amniocentesis, age (≥ 35 years at delivery) was an indication; and of these, only six (5%) had any prior knowledge of genetic risk. During the same time interval, 188 patients over 35 years of age who initiated prenatal care too late for prenatal diagnosis were counseled in the hospital after delivery: 101 (54%) indicated that they would have accepted amniocentesis. The conclusion was that (1) genetic services are acceptable to this socioeconomic group, and (2) accessibility and publicit are needed to promote utilization in this population. (AM. J. OBSTET. GYNECOL. 138:11, 1980.)

THE RECOGNITION of amniocentesis as a safe vehicle for in utero diagnosis of many fetal defects<sup>1, 2</sup> has been accompanied by an exponential rise in the number of procedures and diagnoses. However, the greatest usage of these services has been by patients with higher incomes and greater educational achievement.<sup>1, 3</sup> We report our experience in an obstetric-care program lo-

From the Department of Pediatrics, Division of Medical Genetics, and the Department of Gynecology and Obstetrics, Emcry University School of Medicine; and the Maternal and Infant Care Project, Grady Memorial Hospital.

Supported by Grant MCG 310001-01 from the United States Public Health Service and by a grant from the Georgia Department of Human Resources.

Presented in part at the Thirtieth Annual Meeting of the American Society of Human Genetics, Minneapolis, Minnesota, October 3-6, 1979.

Received for publication March 11, 1980.

Accepted April 21, 1980.

Reprint requests: J. P. Marion, Department of Pediatrics, Division of Medical Genetics, Emory University School of Medicine, 69 Butler St., Atlanta, Georgia 30303. cated in Grady Memorial Hospital, the urban Atlanta city-county hospital used principally by low-income, Black patients. We identified, counseled, and offered amniocentesis to those pregnant women who were at risk for genetic defects amenable to prenatal diagnosis. We also examined those factors that have contributed to the heretofore low rates of amniocentesis in this so-cioeconomic group.

### Methods

Before the inception of this genetic-obstetric clinic, all pregnant patients who requested prenatal care at Grady Memorial Hospital were interviewed by examiners trained to review the patients' medical records and to obtain detailed medical histories. Women with any high-risk factor which would have affected the pregnancy adversely were then evaluated in one of several specialized obstetric clinics of the Maternal and Infant Care Project. We modified this process by training the interviewers to refer to the genetic-obstetric clinic all patients who met any of the following criteria for genetic risk: (1) maternal age of 35 or over at deliv-

Table I. Grady Memorial Hospital obstetric population

	No. of deliveries				
Obstetric categories	1975	1976	1977		
All Fulton and DeKalb County residents	14,775	15.139	15,278		
Grady Memorial Hospital—all races	5,234 (36%)*	5,384 (36%)*	5,605 (37%)*		
Grady Memorial Hospital-black	4,362 (83%)†	4,446 (83%)†	4,639 (83%)†		
Grady Memorial Hospital—all women ≥35 yr at delivery	,,	, , , ,	, , , , , , , , , , , , , , , , , , , ,		
Early prenatal care (≤20 postmenstrual weeks)‡	59 (37%)	72 (43%)	59 (36%)		
Late prenatal care (>20 postmenstrual weeks)‡	71 (44%)	65 (39%)	80 (48%)		
No prenatal care	31 (19%)	31 (18%)	26 (16%)		
Totals	161 (100%)	168 (100%)	165 (100%)		

<sup>\*</sup>Percentage of Fulton and DeKalb County residents who were delivered of infants at Grady Memorial Hospital.

Table II. Acceptance or rejection of amniocentesis (advanced maternal age vs. other indications)

	1976 (Second half)			1977		1978						
					d half	First half		Second half		Total		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Advanced maternal age (≥35 years) at delivery				-					,			
Accepted	5	36	8	62	16	57	24	59	15	63	68	57
Rejected	_9	64	_5	38	$\frac{12}{28}$	43	<u>17</u>	41	9	47	_52	43
Total	14		13		28		41		$\frac{9}{24}$		120	
Family history of genetic defect*												
Accepted	2	67	4	57	5	83	4	67	12	80	27	73
Rejected	<u>1</u>	33	$\frac{3}{7}$	43	<u>1</u>	17	<u>2</u>	33	_3	20	$\frac{10}{37}$	27
Total	3		7		$\frac{1}{6}$		6		15		37	
All indications												
Accepted	7	41	12	60†	21	62	28	60	27	69	95	61
Rejected	$\frac{10}{17}$	59	_8_	40	13	38	<u>19</u>	40	<u>12</u>	31	_62	39
Total	17		20		34		47		39		157	

<sup>\*</sup>Included patients identified with family history of a chromosome defect (n = 15), neural tube defect (n = 16), or X-linked recessive defect (n = 6).

ery, (2) family history of chromosome abnormality, (3) family history of neural tube defect or vertebral anomaly, (4) family at risk for an X-linked recessive, autosomal recessive, or autosomal dominant disorder, and (5) history of three or more spontaneous abortions. Referrals also came from individual housestaff physicians, other clinics, and patients who inquired about the genetic-obstetric clinic after postpartum counseling.

At the first genetic-obstetric clinic visit, all new patients were informed of the reason for referral and were asked whether they were aware of any increased risk for their offspring (termed prior knowledge). An answer of "yes" or "no" was used to classify patients' prior knowledge, on the basis of their response and assessment by the counselor. History and pedigree were constructed, necessary medical records were obtained, and affected family members were examined. When prenatal genetic diagnosis was indicated, eligible

women were counseled in regard to their chances for affected offspring and about the risks, benefits, and options of all procedures. Patients who agreed to amniocentesis were required to give informed consent.4 The clinic was staffed by two M.D.-geneticists (one an obstetrician), two masters-level genetic counselors, and an obstetric nurse with genetic training. Nearly all amniocenteses were performed by the clinic obstetriciangeneticist (G. K.). Sonography was used for localization of the placenta, estimation of gestational age, identification of multiple births, and placement of the needle before and during the amniocenteses. Three fourths of the specimens of amniotic fluid were cultured by the Cytogenetics Laboratory, Division of Medical Genetics, Emory University. The remainder were cultured by the Cellular Genetics Laboratory, Pathology Division, Bureau of Laboratories, Center for Disease Control. Concentrations of alpha fetoprotein were

<sup>†</sup>Percentage of black women delivered of infants at Grady Memorial Hospital.

<sup>‡</sup>Calculated by patient report of last menstrual period and date of first entry interview.

<sup>†</sup>Onset of peer support was during this period. (See Methods.)

Duing by and day	Chaire magadina	Advanced maternal age (≥35 yr)		Genetic defect in family*		Totals	
Prior knowledge of genetic risk	Choice regarding amniocentesis	No.	(% Accept)	No.	(% Accept)	No.	(% Accept)
Yes	Accept Refuse	4 >	(67)	12>	(86)	$^{16}_{4}>$	(80)
No	Accept Refuse	$^{64}_{50}$ $>$	. (56)	$^{15}_{8}>$	(65)	$^{79}_{58}$ $>$	(58)
	Totals	$\frac{120}{120}$	(57)	<del>37</del>	(73)	157	(61)

Table III. Response of eligible antepartum patients who were offered amniocentesis

determined in the laboratory of Dr. Aubrey Milunsky, E. K. Shriver Center for Genetic Research, Waltham, Massachusetts.

All patients who underwent amniocentesis were retained in the genetic-obstetric clinic for the duration of their antepartum care. During early 1977, when this clinic had been in operation for about half a year, several patients who had initially declined amniocentesis changed their minds and decided to accept it. This change occurred after they had talked to patients in the waiting room who had already undergone amniocentesis. When we observed this positive effect on acceptance, we instituted peer support as a regular practice.

### Results

Eligibility for delivery care at Grady Memorial Hospital is determined by residence in Fulton or DeKalb counties, which are the two largest counties in Georgia and contain the greatest population mass of metropolitan Atlanta. The demography of this obstetric population for 1975 through 1977 is outlined in Table I and emphasizes that more than one third of the patients who resided in these two counties were delivered of infants at Grady Memorial Hospital. Eighty-three percent of these patients were black. Ninety percent had a total family income of less than \$10,000 per annum. When the clinic was established, we assumed that advanced maternal age would constitute the main indication for prenatal monitoring, since 3% of all deliveries at Grady Memorial Hospital were to women who were 35 years of age and older. However, because nearly two thirds of these patients first initiated prenatal care in the second half of gestation or at delivery (Table I), we anticipated that a large group could not be referred in time for prenatal genetic diagnosis.

During the study interval beginning in August. 1976, and extending through December, 1978, 522 patients were evaluated and counseled in this genetic-obstetric clinic. One hundred fifty-seven patients were offered prenatal monitoring. As anticipated, most (120, or 76%) were referred because of advanced maternal age;

the remainder had a chromosomal or genetic defect in the family. Ninety-five (61%) of the eligible patients elected amniocentesis (Table II, lower right). There was an increase in the rate of acceptance of amniocentesis from 41% during the last half of 1976, to 69% during the last half of 1978. The percentage of patients who underwent amniocentesis changed most dramatically in the first half of 1977, during and after the time when peer support in clinic counseling sessions was initiated. To evaluate whether the indication for amniocentesis affected the rate of acceptance, counseled patients were divided into two general categories those of advanced age and those who had a history of genetic defect in the family (Table II). Comparison of these two groups revealed that the patients who had a genetic defect in the family had higher initial and overall rates of acceptance of amniocentesis. This group also had a less striking increase in the rate of acceptance during the period of study.

We investigated the relationship between acceptance of amniocentesis, indication (advanced age or genetic defect in the family), and prior knowledge of an increased genetic risk for the pregnancy (Table III). The three-dimensional frequency table of results was analyzed with the use of log-linear models.<sup>5</sup> The specific relationship between prior knowledge and acceptance, adjusted for the relationship between prior knowledge and indication, was highly significant (p < 0.0001). Thus, there was strong evidence that prior knowledge increased acceptance of amniocentesis. Women who had genetic defects in the family were more likely to have had prior knowledge of risk than women for whom age was an indication. Very few older women (6 of 120, or 5%) were aware of any genetic risk, prior to counseling.

Among the 157 patients who were offered amniocentesis, educational achievement was known for 119. Five finished no more than the sixth grade, 100 had between 7 and 12 years of schooling, and 14 completed more than the twelfth grade. Twelve of the 14 (93%) who had had education past the twelfth grade accepted amniocentesis. Rates of acceptance were 60% &

<sup>\*</sup>As defined for Table II.

**Table IV.** Reasons for declining amniocentesis

Moral issues:		21
Would not abort a defective fetus	13	
Religion forbids this testing	3	
Wants baby regardless of any defects	5	
Fear:		13
Scared of needle	6	
Afraid of abortion from this test	4	
Don't want to know	3	
External opposition:		10
Husband/father of child opposed	7	
Other relative opposed	3	
Other issues:		3
Do not believe anything will go wrong	2	
Risk not high enough	1	
Total providing a response		47
Total refusing to provide a response		15
· , · ·		CO
Total No. of patients declining		62

Table V. Response of older patients (≥35 yr) who were counseled after delivery

Prior knowledge of genetic risk	Choice regarding amniocentesis	No. of patients	Percent acceptance
Yes	Accept Refuse (or unde- cided)	12/3>	80
No	Accept Refuse (or unde- cided)	89 84>	51
	Totals	188	54

and 62%, respectively, for those who had completed no more than the sixth grade and those who had completed any grades from 7 through 12. White patients had a higher overall rate of acceptance (21 of 29, or 72%) than black patients (74 of 128, or 58%). The mean parity of all patients who rejected amniocentesis was 7, compared to 3 for patients who accepted.

We wanted to know why women rejected amniocentesis. Their reasons for declining are shown in Table IV. Most women cited moral concerns or reluctance to interfere in any decisive way with progression of the pregnancy, even if the fetus were abnormal. Fear of injury to oneself or to the fetus or of learning unpleasant news was the second most frequent reason. Several patients declined amniocentesis because either an influential member of the family or the mate was opposed to the procedure. One quarter of the patients refused to provide a response and stated no more specific reason for declining amniocentesis than "I just don't want it."

During the period of our study, 281 of 401 (70%) patients of advanced maternal age initiated obstetric care too late for prenatal diagnosis. As a consequence, the overall usage rate of amniocentesis by these older

patients who were delivered of infants at Grady Memorial Hospital was only 17% (68 of 401). We wanted to examine whether these women who came too late for amniocentesis would have been equally accepting of it. In the hospital after delivery, we counseled 188 patients who were 35 years of age and older who (I) were delivered of normal infants and (2) did not have tubal ligation after delivery. The results are summarized in Table V. The majority (101) declared that they would accept amniocentesis for a subsequent pregnancy, or would have undergone amniocentesis prior to this delivery if they had been aware of the service. Nine said "no," and 78 were undecided. If the postpartum patients who were undecided are counted as negative responses, 54% would have elected amniocentesis. This figure was similar to the actual acceptance rate of 57% among the eligible patients of older age who came in time for amniocentesis (see Table II).

### Comment

Prior to initiation of the special genetic-obstetric clinic, only five patients who were delivered at Grady Memorial Hospital received prenatal genetic diagnosis during the 3 years after techniques of amniocentesis, cell culture, and karyotyping were developed at Emory University. Since other workers have indicated poor utilization of prenatal diagnosis among lower socioeconomic groups, it was reasonable to predict that prenatal monitoring might have been largely rejected by our eligible patients. However, we found an initial 41% rate of acceptance, which increased to 69% at the end of the study period. Several noteworthy factors may have contributed to this rate of acceptance: (1) immediate referral of eligible patients at the first point of patient contact, rather than reliance on recognition of a patient's increased risk during the regular course of antepartum care; (2) direct education of each patient in a genetic counseling session within the comprehensive obstetric-care system; and (3) a plan for new patients to discuss amniocentesis with patients who had already undergone the procedure.

Despite the increasing acceptance of amniocentesis among counseled patients, the overall utilization rate among all patients 35 years of age and older in our study was only 17%. However, this low rate of use was not limited to the patients at Grady Memorial Hospital. Subsequent to a concerted educational program for physicians in the seven-county greater Atlanta metropolitan area, only a 16% utilization rate was achieved for all women who were 35 years of age and older at the time of delivery. Our present study demonstrated that two major factors were associated with a low rate of

utilization of amniocentesis services by older patients in our study. One factor was a delay in seeking antepartum care. The second was a poor awareness of increased genetic risk for the pregnancy. Both problems indicate a need for education directed toward the patient, as well as toward the physician. The goal of this proposed educational process should be to increase awareness among older women of the higher risk to their offspring and to encourage early prenatal care so that amniocentesis can be offered.

Whether delay on the part of the patient in seeking prenatal care can be changed is not known. Noncompliance for health care delivery is a well-known problem which is not yet solved. 6, 7 However, the counseling program described in this report was initiated with no prior publicity in the community. We believe that a concerted educational program directed toward the patient in regard to genetic risk and available alternatives would increase the patient's awareness and use of genetic services in this urban community.

We wish to thank Dr. Brent Blumenstein, Department of Biometry, Emory University, for statistical consultations, and Kathy Perrodin, Department of Patient Records and Data Management, Maternal and Infant Care Project, Grady Memorial Hospital, for data retrieval and assembly.

### REFERENCES

- 1. Midtrimester Amniocentesis for Prenatal Diagnosis: Safety and Accuracy, National Institute of Child Health and Human Development, National Registry for Amniocentesis Study Group, J.A.M.A. 236:1471, 1976.
- 2. Simpson, N. E., Dallaire, L., and Miller, J. F.: Prenatal diagnosis of genetic disease in Canada. Report of a collaborative study, Can. Med. Assoc. J. 115:739, 1976.
- 3. Golbus, M. S., Loughman, W. D., Epstein, C. J., Halbasch, G., Stephens, J. D., and Hall, B. D.: Prenatal genetic diagnosis in 3,000 amniocenteses, N. Engl. J. Med. 300:157,
- 4. Oakley, G. P., Brantley, K., Chen, A. T. L., Fernhoff, P. M., Goldberg, M. F., Priest, J. H., and Trusler, S.: A
- community approach to prenatal diagnosis, in Hook, E. B., and Porter, I. H., editors: Service and Education in Medical Genetics, New York, 1979, Academic Press, Inc., pp.
- 5. Bishop, Y. M., Fienberg, S., and Holland, P. W.: Discrete Multivariant Analysis: Theory and Practice, Cambridge, 1975, Massachusetts Institute of Technology Press.
- 6. Becker, M. H., and Green, I. W.: A family approach to compliance with medical treatment: A selective review of the literature, Int. J. Health Educ. 13:1, 1975.
- 7. Becker, M. N., and Maimau, L. A.: Sociobehavioral determinants of compliance with health and medical care recommendations, Med. Care 13:10, 1975.

## Myomas of the uterus in pregnancy: Ultrasonographic follow-up

DAVID MURAM, M.D.
MARTIN GILLIESON, M.B., F.R.C.S.(C.)
JACK H. WALTERS, M.D.
Ottawa, Ontario, Canada

A review was made of the medical records of pregnant patients who had myomas that were documented by ultrasonographic studies. Only 42% of the myomas were diagnosed by physical examination. In most instances the clinical diagnosis was made when the neoplasm was large. However, when the myoma was 3 cm to 5 cm in diameter, the rate of detection on physical examination was only 12.5%. The relationship between the location of the myomas and the placental site emerged as a significant prognostic clue to the outcome of the pregnancy. Ten of 13 patients in whom there was contact between the two presented with complications of pregnancy, mainly antepartum bleeding and premature rupture of membranes. A prospective study is currently in progress. (AM. J. OBSTET. GYNECOL. 138:16, 1980.)

ACCORDING to reports of several large series, 1-4 the incidence of myomas of the uterus in pregnancy ranges between 0.3% and 2.6%. The low figure suggests that the majority of myomas are asymptomatic; even in pregnancy, and hence, escape detection. The finding of uterine myomas in 50% of autopsies<sup>5</sup> emphasized the common occurrence of these neoplasms. The clinical evaluation of small, symptom-free myomas of the uterus is often subjective and not always simple. Because of the pregnancy, the physician tends to avoid an invasive investigation. Among the complications of pregnancy ascribed to myomas are a decreased fertility, increased incidence of abortions, ectopic pregnancy, 6, 7 red degeneration, disseminated intravascular coagulation, 8, 9 hemoperitoneum, 10 premature rupture of membranes, 11 dystocia secondary to cervical myoma, 3 extrusion of the myoma, inversion of the uterus, 1, 12 and postpartum hemorrhage.9

### Material and methods

The introduction of ultrasonography to the field of obstetrics gave the physician an opportunity to docu-

From the Department of Obstetrics and Gynecology, and the Ultrasound Section, University of Ottawa.

Received for publication January 22, 1980.

Revised April 7, 1980.

Accepted April 14, 1980.

Reprint requests: Martin Gillieson, M.B., Ottawa General Hospital, 43 Bruyere St., Ottawa, Ontario, Canada KIN 5C8. ment the presence of myomas in the uterus, to measure them, and to follow them throughout pregnancy. In a retrospective study, we reviewed the medical records of about 5,000 obstetric patients who had undergone at least one ultrasonographic examination at the Ottawa General Hospital over a period of 2½ years between 1976 and 1978. All ultrasonographic screening was performed by the same examiner, with the use of a Picker Echoview XI with EDC gray scale adaptation. Many patients were also studied by means of an Advanced Diagnostic Research real-time machine, but the size of the myomas and the placental site were always diagnosed by means of the storage gray-scale technique.

Diagnosis of myomas was made when the following criteria were fulfilled: (1) A mass greater than 3 cm in diameter was observed. (2) The mass was spherical. (3) The myometrial contour was distorted by the mass, either externally or by impingement on the gestation sac. (4) The mass was of different acoustical structure than the myometrium.

All masses fulfilling these first four criteria were subjected to further study at varying ultrasound sensitivities in order to bring out their structure. Internal echoes were studied carefully in order to differentiate them from reverberation artifacts.

Two more criteria were added after this detailed study: (1) The mass showed a speckled pattern of internal echoes, increasing in density with an increased ultrasound sensitivity. (2) No enhancement of echoes was noticed behind the mass, which would have suggested a cystic nature.

**Table I.** Relationship between location of myomas and their clinical detection

Location of myomas	No. of patients	Clinically detected
Isthmus uteri	1	1.
Corpus uteri, anterior surface	21	8
Corpus uteri, posterior surface	14	6
Fundus uteri	2	2 ·
Cornua uteri	3	3

The placenta was localized by means of the usual well-established criteria.13 Patients were rescanned at varying intervals for indications, such as estimation of growth patterns, etc., to evaluate growth of the myomas.

If more than one myoma was diagnosed, the largest one was considered to be representative. There were 51 patients in whom a definite diagnosis of myomas of the uterus was made, and 41 of them were followed until the termination of the pregnancy. Of the other 10 patients, six moved to other cities and four had therapeutic abortions.

In 13 of the patients the ultrasonographic diagnosis was confirmed by pathologic examination. In six patients the myomas were seen at the time of cesarean section, and in one of them a myomectomy was performed at that time. Four of the remaining 13 patients underwent abdominal hysterectomy, and the presence of myomas was confirmed by the pathologist. In the other three patients, the myomas were visualized at the time of laparotomy. The indications for laparotomy were adnexal disease in two patients and tubal ligation in one.

### Results

Age, parity, and race of the patients. The patients ranged in age between 24 and 41 years, with an average of 31 years. Sixteen of the patients were under the age of 30 years, and only one patient was older than 39 years. There were 25 primigravidas and 16 multiparas. Only five of 41 patients were not Caucasians. Three were Blacks, and two were Indians.

Clinical detection of myomas of the uterus during pregnancy. In 17 of 41 patients (41%), the myomas were diagnosed by the referring physician. Small myomas escaped clinical detection frequently, whereas large ones were detected with relative ease.

Sixteen patients had small myomas, 3 cm to 5 cm in diameter, only two of which (12.5%) were diagnosed clinically. Twenty patients had a medium-sized myomas, between 5 cm and 10 cm in diameter, 11 of which were diagnosed on physical examination. Five patients had large myomas, more than 10 cm in diameter, four

Table II. Relationship between size of myomas and method of delivery

	Si			
Method of delivery	3 to 5 cm in diameter	cm in	10 cm or more in diameter	Total
Vaginal delivery	12	14	3	29
Cesarean section	1	4	2	7
Spontaneous abortion	3	2		5

Table III. Relationship between myoma and placental site

	Location of placenta					
Size of myoma	No contact between myoma and placenta	Margin of placenta in contact with myoma	Partial or complete overlapping			
3 to 5 cm 5 to 10 cm	10 15	6 8				
>10 cm Total	$\frac{3}{28}$	$\frac{1}{10}$	$\frac{1}{3}$			

of which (80%) were diagnosed prior to the ultrasonographic examination.

Location of the myomas and clinical detection of them. Thirty-five of 41 patients had a myoma on the corpus uteri. In 21 of these patients the neoplasm was on the anterior surface of the uterus, and in 14 it was on the posterior surface. The myoma was on the cornua in three patients, on the fundus in two, and on the isthmus in one. In the latter six patients the diagnoses were made on physical examination. The rate of detection was lower when the neoplasm was on the corpus uteri. In only eight of 21 patients with the myoma on the anterior surface of the uterus, and in six of 14 patients with the myoma on the posterior surface were the tumors found by physical examination (Table I).

Changes in size of myomas during pregnancy. In 38 of 41 patients there was no demonstrable change in size of the myoma. In two patients the size of the myoma increased by 20% and 25%. In one patient the neoplasm diminished in size by 20%.

Abortion. Five patients aborted spontaneously: four of them in the first trimester, and one patient at 16 weeks' gestation. The overall incidence of abortion was 12%. The abortion rate appears not to have been increased.

Fetal growth. The incidence of small-for-dates infants was similar to the general figures. Three infants were below the tenth percentile for gestational age, 17 were in the tenth to fiftieth percentile for gestational .

Patient	Size of myoma	Relationship between myoma and placental site	Week of gestation	Complication of pregnancy	Pregnancy outcome
н. ј.	Small	Contact	8	Bleeding	Abortion
M. Ľ.	Small	Contact	· 10	Bleeding	Normal vaginal delivery
P. I.	Small	Contact	- 11 .	Bleeding	Abortion
A. S.	Medium	Overlapping	11	Bleeding	Abortion
R. I.	Medium	Overlapping	16	Bleeding	Abortion
N. R.	Medium	Contact	26	Premature rupture of membranes	Delivery .
G. L.	Small	Contact	33	Premature rupture of membranes	Delivery
R. B	Medium	Contact	33	Premature rupture of membranes	Delivery
M. L.	Large	Contact	38	Bleeding	Cesarean section
S. L.	Small	Contact	Post partum	Hemorrhage	MATERIAL
H. C.	Medium	Contact	40		Normal vaginal delivery
C. L.	Small	Contact	40	·	Normal vaginal delivery
D. A.	Large	Overlapping	40		Normal vaginal delivery

Table IV. Course of pregnancy in patients in whom there was contact between myoma and placenta

age, and 16 were in the fiftieth to ninetieth percentile for gestational age. Fetal growth appears not to have been affected by the presence of myomas.

Method of delivery. Twenty-nine of 36 patients who carried to viability had a vaginal delivery. The other seven patients were delivered of infants by cesarean section, an incidence of 17%. The indications for abdominal delivery were as follows: previous cesarean section in two cases, and one each because of extensive myomectomy, breech presentation in a primigravida, placenta previa, fetal distress, and cephalopelvic disproportion. The size of the myoma did not appear to affect the method of delivery (Table II).

Relationship between size of myoma and placental site. In 28 of 41 patients, there was no contact between the margin of the placenta and the myoma. In these patients the placenta was implanted on the opposite wall of the uterus.

In 10 of 41 patients the placenta was implanted on the same uterine wall as the myoma, and the placental margin was in contact with the myoma. In three patients the placenta was located directly over a myoma (Table III).

In 13 patients there was contact between the myoma and the placenta. A significant observation was that 10 of these patients had complicated pregnancies. The complications included premature rupture of membranes, bleeding during pregnancy, and postpartum hemorrhage; the three patients with these complications had no problems during gestation and labor, even though in one case the myoma was large and the placenta was situated directly over the myoma (Table IV).

### Comment

The problems of ultrasonic diagnosis of myomas which complicate pregnancy are considerable. In the ·first trimester they may be confused with a corpus luteum, cystic teratoma of the ovary, other benign or malignant tumors of the ovary, and, more rarely, the nonpregnant cornua of a bicornuate uterus.11 In view of this, no patient was included in this study on the basis of a first-trimester scan alone.

Myomas often show bizarre internal structure, and may be more or less transonic than the myometrium. Nevertheless, solid tumors of the ovary or uterus which might be confused with myomas are rare, and we doubt that any have been inadvertently included in the study.

In the last 2 years, we were able to confirm pathologically or anatomically the presence of myomas in 13 patients. This confirmation emphasizes the accuracy of the ultrasonographic diagnosis.

In this series, the incidence of myomas complicating pregnancy was less than 1%. Clinical detection of the myomas depended on their size and location. Only two of the 16 myomas that were 3 cm to 5 cm in size were found by physical examination, whereas there was a pick-up rate of 80% when the myoma was larger than 10 cm in diameter.

All the fundal, cornual, and isthmic myomas were detected clinically. Myomas that were situated on the corpus uteri often escaped detection. The overall rate of clinical diagnosis was 42%.

It is interesting to note that most of the patients were Caucasians. The average age and parity in this series were not different from those in other series.1, 4 Fetal growth and method of delivery were not affected by the presence of myomas.

We were able to correlate not only the size of the myomas with the outcome of pregnancy, but also the relationship between the placental site and the myoma. This latter association appears to be significant in view of the multiple complications in the patients in whom the placental site was in contact with a myoma.

Even though the number of patients was small, the findings suggest that patients in whom the placental site is near a myoma form a special subgroup which is at risk for complications, such as premature rupture of membranes, antepartum bleeding, and postpartum hemorrhage.

This study indicates that the location of the myoma, especially its relationship to the placental site, is more significant than its actual size in predicting pregnancy outcome. The ultrasonic technique enables one to visualize myomas, measure them accurately, and follow them throughout pregnancy without harming the mother or the fetus. Patients in whom there is a close

proximity between myoma and placental site seem to be at greater risk and should be followed more carefully. Since only ultrasonographic study can determine the relationship between the myoma and the placental site, every pregnant patient with suspected myoma should be scanned. We are now conducting a prospective study to assess our findings.

We wish to thank Dr. H. Oxorn for his advice and encouragement.

#### REFERENCES

- 1. Chassar Moir, J., and Myerscough, P. R.: Fibromyomata of the uterus, in Kerr, M., editor: Operative Obstetrics, London, 1971, Bailiére, Tindall Cassell, Ltd., chap. 18, ор. 398-421.
- 2. Davids, A. M.: Fibromyomas, in Rovinski, J. J., and Gutmarche, A. F., Medical, Surgical and Gynecologic Complications of Pregnancy, Baltimore, 1965, The Williams & Wilkins Co., chap. 28, pp. 366-382.
- 3. Douglas, R. G., and Stromme, W. B.: Operative Obstetrics, New York, 1976, Appleton-Century-Crofts, p. 413.
- 4. Tisne, L., and Anselmo, J.: Contribucion al estudio sobre mioma y estado gravido puerperal, Bol. Soc. Chile Obstet. Ginecol. 20:178, 1955.
- 5. Mattingly, R. F.: In Te Linde, R., editor: Operative Gynecology, Philadelphia, 1977, J. B. Lippincott, Co., p. 187.
- Dees, H. C.: Cervical pregnancy associated with uterine leiomyomas, South. Med. J. 59:900, 1966.
- Hepperlen, H. M.: Ectopic pregnancy associated with fibromyoma, Nebr. Med. J. 55:428, 1970.
- 8. Hnat, R. F., Anderson, G. G., and Alonzo, D. R.: Diffuse

- intravascular coagulation associated with a degenerating myoma during pregnancy, Obstet. Gynecol. 29:207,
- 9. Moore, J. B., and Morton, D. G.: Leiomyomas of the uterus, in Sciarra, J. J., and McElin, T. W., editors: Gynecology and Obstetrics, Hagerstown, 1979, Harper & Row, Publishers, vol. I, chap. 26, pp. 1-11.
- 10. Buttery, B. W.: Spontaneous haempoeritoneum complicating uterine fibromyoma, Aust. N. Z. J. Obstet. Gynaecol. 12:210, 1972.
- 11. Von Mickey, L. I.: Sonographic study of uterine fibromyomata in the non-pregnant state and during gestations, in Saunders, R. D., and James, A. E., editors: Ultrasonography in Obstetrics and Gynecology, New York,
- 1977, Appleton-Century-Crofts, chap. 26, pp. 297-331.

  12. Telko, M., Powlony, M., and Pawlicka, H.: Diagnosis and therapy of puerperal eversion of myomatous uterus, Ginekol, Pol. 44:699, 1973.
- 13. Kobayashi, M., Hellman, L. M., and Fillisti, L.: Placental localization by ultrasound, Am. J. OBSTET. GYNECOL. 106:279, 1970.

## Plasma oxytocin levels and disappearance rate after buccal Pitocin

M. YUSOFF DAWOOD, M.D., M.MED., M.R.C.O.G., F.A.C.O.G. OLIVA YLIKORKALA, M.D., DR.MED.\*
FRITZ FUCHS, M.D., DR.MED., F.A.C.O.G.
Chicago, Illinois, and New York, New York

Plasma concentrations of oxytocin (OT) were determined by a highly specific and sensitive radioimmunoassay in (1) nine pregnant women near or at term who were given 400 units of buccal OT every 20 minutes to induce labor or to augment uterine contractions; (2) four acult males who were given 200 units and 400 units of buccal OT every 20 minutes in two separate experiments each lasting 2 hours; and (3) three adult males at regular intervals up to 45 minutes after discontinuation of buccal OT. Plasma concentrations of OT increased in all the women studied, and exceeded 50 picograms per milliliter in six of nine patients after buccal OT was given. However, the net increase in OT was less than 50 pg/ml in six of rine patients. In males, 90% of the plasma samples collected when 400 units of OT was given had detectable levels of OT, with mean levels of 24 to 32 pg/ml; when 200 units was used, only 53% of the plasma samples had detectable OT, and mean levels were consistently below 10 pg/ml. Plasma OT decreased to one third but not to baseline levels in the course of 45 minutes after OT was discontinued. The findings indicate that with 400 units of buccal OT every 20 minutes, plasma OT concentrations attained were similar to those found during the first stage of labor, and that the disappearance of OT from the plasma after discontinuation was slow. (Am. J. OBSTET. GYNECOL. 138:20, 1980.)

UNTIL RECENTLY, the use of oxytocin (OT) to initiate or augment uterine contractions in term or near-term pregnancy was widely accepted and firmly entrenched in clinical practice. It was also customary to use the uterine response to "titrate" the dosage of OT needed to achieve the level of rhythmical uterine activity required to expel the fetus. Disagreement exists as to whether a "physiologic" dose, as advanced by some obstetricians, or a "pharmacologic" dose, as advanced by

From the Department of Obstetrics and Gynecology, The Abraham Lincoln School of Medicine, University of Illinois, and Carnell University Medical College.

Supported by grants from Parke-Davis & Company, Basil O'Connor Starter Grant, National Foundation—March of Dimes (M.Y.D.), and Ford Foundation Grant No. 670-0455A.

Received for publication May 14, 1979.

Revised March 5, 1980.

Accepted March 27, 1980.

Reprint requests: M. Yusoff Dawood, M.D., Department of Obstetrics and Gynecology, The Abraham Lincoln School of Medicine, University of Illinois, 840 South Wood St., Chicago, Illinois 60612.

\*Ford Foundation Fellow. Present address: University of Oulu. Finland.

others,<sup>2</sup> should be employed when OT is given by the intravenous route. The risk of uterine hypertonus and rupture necessitates close supervision of the patient and adjustment of the OT dosage. Because the buccal administration of OT is considered to be much easier, it has been used to stimulate the uterus at or near term. Objections have been raised because of the alleged variable and uncontrolled transbuccal absorption rate of OT, and it has been postulated that it takes longer to terminate the effect of buccal OT than that of intravenous OT. However, there are no reports on the OT levels in plasma when either buccal or intravenous OT is given to parturient women to induce or augment uterine contractions, or when buccal OT is given to nonpregnant subjects. The present study was undertaken to determine plasma concentrations of OT when buccal Pitocin\* was given to pregnant women near or at term and to male subjects. It was considered to be useful to determine whether the plasma OT concentrations achieved during buccal administration of Pitocin were similar to or higher than the physiologic levels that we have previously demonstrated in normal spontaneous labor and vaginal delivery,3,4 and the disap-

<sup>\*</sup>Pitocin, Parke, Davis & Company, Detroit, Michigan.

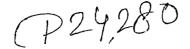


Table I. Plasma concentration of oxytocin measured by radioimmunoassay in nine pregnant women at or near term who were given buccal Pitocin to induce labor or augment uterine contractions

D . d	Cartatia	Time (min)	Total door of	Plasma oxytocin (pg/ml)		
Patient No.	Gestation (weeks)	Time (min) after starting Pitocin	Total dose of Pitocin (units) administered	Before buccal Pitocin	After buccal Pitocir	
1	39	90	0	106.9		
		20	200	_	105.0	
		65	600		126.3	
		95	1,000	_	127.5	
2	35	0	Ď	1.5	<u>—</u>	
		60	1,200	_	2.0	
		120	2,000		29.5	
		180	2,000*	_	23.6	
3	39	0	, j	35.6	_	
		30	400		36.3	
		100	1,600		43.1	
4	40	0	, j	26.1	-	
		20	200		27.5	
		80	1,000	· · ·	78.8	
5	37	0	, O	76.3	_	
		20	400	_	79.7	
6	40	0	0)	33.8	_	
		20	200	_	55.0	
		60	800	_	16.1	
		100	2,000		65.0	
7	40	0	0	8.6	_	
		30	400		40.6	
		85	1,600	_	45.0	
		110	2,000	_	165.0	
8	39	0	Ó	1.5	_	
	÷	60	600	_	1.5	
		120	1,400		10.8	
		300	2,200+		6.8	
9	40	0	. 0	70.0	_	
		20	400		181.3	

<sup>\*</sup>Buccal Pitocin given for 2 hours only and then discontinued.

pearance of OT from the plasma after discontinuation of buccal administration of oxytocin.

### Material and methods

Patients. Nine women between 35 and 40 weeks' gestation were given buccal Pitocin by their obstetricians either to augment uterine contractions or to induce labor for obstetric reasons. All patients gave consent for the study. The management of these patients with respect to the dosage of buccal Pitocin or the mode of delivery was not influenced by the measurement of plasma OT, since all determinations of OT were completed after the delivery, and the individual results were not made available to the clinicians. All patients were voutinely monitored with an external cardiotocograph. •

Four healthy adult males, ages 20 to 59 years, with a body weight of 55 to 70 kilograms volunteered for a study of plasma concentrations of oxytocin before, during, and after administration of buccal Pitocin

Dosage of buccal Pitocin. For the parturient women, buccal Pitocin was given in a dose of 400 units every 20

minutes to be placed on the buccal mucosa. This was the standard dosage employed in the department at the time. Because of recent regulations, the use of buccal Pitocin has since been discontinued. For the adult males, two different dose regimens were used. Initially, a dose of 200 units of buccal Pitocin every 20 minutes was given for up to seven doses. Subsequently, the same volunteers repeated the experiment a week later with a dose of 400 units of buccal Pitocin every 20 minutes until six doses were completed.

Collection of blood and determination of plasma OT. Blood was collected through an indwelling No. 19 G butterfly scalp vein needle inserted into the antecubital vein and maintained open with flushings of diluted heparin (50 units per milliliter of normal saline solution). Samples of blood were collected in all study subjects before the administration of buccal Pitocin. With the male volunteers, additional samples of blood were collected every 20 minutes, just before the next dose of buccal Pitocin was given, and 20 minutes after the last cose was given. With the parturient women, samples of blood were collected 20 to 30 minutes after the first

<sup>†</sup>Buccal Pitocin given for 3 hours only and then discontinued.

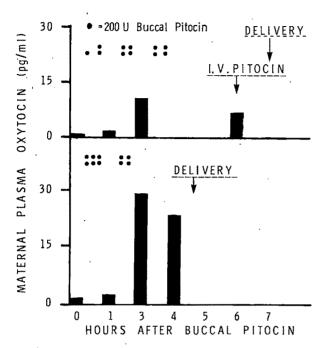


Fig. 1. Maternal plasma oxytocin concentrations in two women given buccal Pitocin (Patients 2 and 8, Table I). Buccal Pitocin was given every 20 minutes, and each dot represents 200 units of buccal Pitocin. Both patients had good, rhythmical uterine contractions, as observed on the continuous external cardiotocograph tracing and were vaginally delivered of infants.

dose of buccal Pitocin, and every hour thereafter until delivery. All samples of blood were collected with chilled heparinized syringes and transferred into chilled heparinized Vacutainers, as previously described.<sup>3</sup> The samples were immediately transported to the laboratory and centrifuged at 4° C; the plasma was separated off and acidified with 1N hydrochloric acid. The acidified plasma was then extracted with Fuller's earth, as previously described.3 The extracted OT was evaporated to dryness and stored at -20° C until measured by a highly specific and sensitive radioimmunoassay, previously described in detail.3 The antibody used was raised in rabbits immunized against oxytocin conjugated to bovine serum albumin and showed less than 0.2% cross reaction with arginine-vasopressin, lysinevasopressin, vasotocin, bovine neurophysin, melanocyte-stimulating hormone, and luteinizing hormone releasing hormone. The sensitivity of the assay was 2.5 pg per assay tube. The intra-assay and interassay coefficients of variation were 7% to 15% and 12% to 18%, respectively. Final recovery due to extraction losses was  $40.5 \pm 0.3\%$ . All results were corrected for recovery.

### Results

Table I shows the OT concentrations in maternal plasma before and during administration of buccal

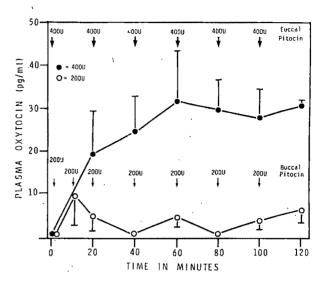


Fig. 2. Plasma oxytocin before and during administration of buccal Pitocin in four adult males. Two different dose regimens, namely, 200 units (o) and 400 units (•) of buccal Pitocin every 20 minutes, were used in two separate experiments. Each point represents the mean ± standard error of plasma oxytocin from four subjects.

Pitocin in nine women at or near term pregnancy. Plasma OT concentrations were less than 40 pg/ml in six of the nine patients, 70 and 76.3 pg/ml in two patients, and 106.9 pg/ml in one patient, before buccal Pitocin was administered. In all patients, plasma OT levels increased after buccal Pitocin but did not exceed 100 pg/ml., except in Patients 1, 7 and 9. In Patients 1 and 9, whose plasma OT exceeded 100 pg/ml, the pretreatment plasma OT levels were 106.9 and 70 pg/ml, respectively and increased to 127.5 and 181.3 pg/ml. In Patient 7, the plasma OT concentration rose from a pretreatment level of 8.6 pg/ml to only 40.6 and 45.0 pg/ml, even after a total dose of 1,600 units of Pitocin, but then jumped to 165 pg/ml after 110 minutes with an additional dose of 400 units of buccal Pitocin. Fig. 1 shows the maternal plasma OT concentrations in two women (Patients 2 and 8, Table I) given buccal Pitocin to induce labor.

Within the limits of the techniques employed, the uterine contractions observed on the continuous external tocograph, as well as by palpation of the uterus throughout buccal administration of Pitocin and during labor in these nine women, showed no evidence of uterine hypertonus. The uterine contractions were regular and rhythmical and lasted 30 to 45 seconds.

In all the males studied, pretreatment plasma OT was undetectable. With 200 units of buccal Pitocin given every 20 minutes in four adult males, plasma OT was detectable in only 15 of 28 samples (53.4%) after up to 2 hours of administration of Pitocin. The plasma

OT concentrations reached had no relationship to the duration of administration of Pitocin. The mean OT concentrations 10 to 120 minutes after the start of buccal Pitocin ranged from 0.2 to 9.9 pg/ml (Fig. 2).

When 400 units of buccal Pitocin was given every 20 minutes to the same four adult males, 20 of the 23 samples collected after the start of buccal Pitocin had detectable plasma OT concentrations (90%). The mean levels of plasma OT attained between 20 and 100 minutes of buccal administration of Pitocin were 24.5 and 31.5 pg/ml (Fig. 2). There was individual variability in the plasma OT concentrations reached, with one subject consistently achieving a much higher plasma OT concentration. None of the males who were studied experienced any side effects with the buccal OT.

The changes in plasma OT concentrations after buccal Pitocin was discontinued are shown in Fig. 3. Plasma OT concentrations during administration of 400 units of buccal Pitocin are similar to those found in Fig. 2. One minute after removal of the buccal tablets and rinsing of the mouth, plasma OT increased to 35.1 ± 9.4 pg/ml (mean  $\pm$  SE), and then declined to 19.7  $\pm$ 5.7 pg/ml at 20 minutes and to  $11.5 \pm 2.5$  pg/ml at 45 minutes.

### Comment

Buccal administration of oxytocin became popular in the years subsequent to the pioneering work of duVigneaud and collaborators<sup>5</sup> on the structure and synthesis of oxytocin. Some of the early clinical trials were carried out by Dillon and associates6 in our department. This form of administration became popular because it permitted the patient to remain ambulatory. The claim was made that the absorption through the buccal mucosa was slow and that removal of the tablets and rinsing of the mouth would interrupt it, thus making this route of administration simple and safe. On the other hand, the rate of absorption was thought to be unpredictable and, therefore, overdosage could easily occur. Although hyperstimulation was undoubtedly possible, the belief was that, generally, with proper supervision of the patient, buccal Pitocin was a useful part of the obstetric armamentarium.

Newman and Hon7 studied the relative effectiveness of the transbuccal and intravenous routes of administration of oxytocin. The effect was measured by quantitation of the uterine activity by means of intrauterine pressure recording. The patients were given alternatingly transbuccal and intravenous oxytocin for induction or augmentation of labor. A considerable variation in the equivalent dosage was found. Thus, 10 milliunits intravenously gave the same uterine response as transbuccal doses of 475 to 1,200 international units in four

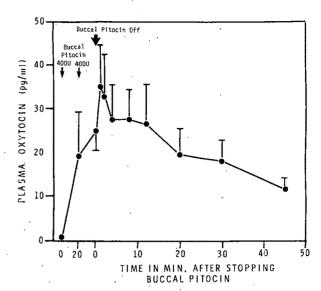


Fig. 3. Mean ± standard error of plasma oxytocin from three adult males before, during, and up to 45 minutes after discontinuation of buccal Pitocin. Plasma oxytocin levels declined slightly during the first 4 minutes, remained the same over the next 8 minutes, and then declined very slowly. The estimated apparent half-life of buccal Pitocin is about 30 minutes.

gatients. The time for the uterine activity to decrease 50% after withdrawal of oxytocin varied from 5 to 25 minutes, with little difference between the two modes cf administration.

Noriega-Guerra and associates 8 also used the uterine response to evaluate buccal oxytocin, with recording of the latent period, maximum effect, time to maximum effect, duration of effect, and disappearance time. In accordance with clinical observations, all parameters showed great variations. It is clear from these two studies and countless clinical observations that uterine activity depends both on the plasma levels of oxytocin and intrinsic factors in the myometrium.

Since the uterine response to oxytocin is so variable, a method of evaluation is measurement of the blood levels of oxytocin after buccal administration. Until the present decade, measurement of OT concentrations was by bioassay methods which suffered from a relative lack of specificity and sensitivity, and which required such large amounts of blood that serial sampling over a short period of time was impossible. The development of radioimmunoassay (RIA) for oxytocin has changed this. The RIA developed in our laboratory is highly specific and sensitive and has permitted serial measurements of plasma oxytocin in the same subject over a short period of time.3

This is the first documentation of the plasma concentrations of oxytocin achieved after buccal administration of Pitocin. It showed that the net increase in OT

concentration was less than 50 pg/ml in six of nine patients when buccal oxytocin was given in the dose regimen employed in this study. It also showed considerable variation from subject to subject. In individual subjects the level usually increased during the duration of treatment, but the values varied considerably. This was particularly true in the pregnant patients and was not surprising in view of the minute-to-minute variations in the endogenous levels found in our previous study. The net increase in circulating OT concentration was more than 100 pg/ml in two of the nine patients (Patients 7 and 9) but was otherwise of the same magnitude as the mean levels of endogenous OT in the first stage of labor which was previously reported by us to be 40.3 ± 9.8 pg/ml.<sup>3, 4</sup>

In the male subjects who were given 400 units of buccal Pitocin every 20 minutes, the mean levels achieved ranged from 24.5 to 31.5 pg/ml, which was similar to the levels achieved with buccal Pitocin in the pregnant patients. As seen in Fig. 2, the concentrations increased during the first hour and then leveled off during continuous treatment. With 200 units every 20 minutes the levels remained very low. Unless the disappearance rate in nonpregnant subjects was related to dose, we have no explanation for this observation.

The disappearance of oxytocin from the plasma was consistently slower after buccal Pitocin than after intravenous oxytocin. With intravenous oxytocin, the estimated apparent half-life in the human being ranges from 3.2 to 5.0 minutes,<sup>10, 11</sup> but using constant infusion rates of oxytocin of either 132 or 256 mU per minute and achieving steady-state concentrations, we

calculated an average half-life of 10.3 ± 1.6 minutes in eight healthy men. 12 A steady-state concentration is more difficult to achieve with buccal than with intravenous oxytocin. Nevertheless, the half-life with buccal oxytocin can be estimated to be about 30 minutes. The longer half-life with buccal Pitocin, compared to intravenous oxytocin, could be due to continuing transfer from the buccal tissues to the blood after removal of the buccal tablets, or to the lower plasma concentrations reached. The half-life of oxytocin has been shown to be longer when a higher dose of intravenous oxytocin was used. 10, 12 The plasma level remained elevated at more than 20 pg/ml for up to 12 minutes after removal of the tablets (Fig. 3), which supports the hypothesis that continued uptake could account for the prolongation of the half-life.

In conclusion, the present study has shown that, when a standard dose of 400 units of buccal Pitocin is given every 20 minutes to pregnant women at term and in labor, and to male subjects, the oxytocin concentrations in the blood are well within the range found during normal "spontaneous" labor, although the levels vary considerably. This is in agreement with the clinical observations of the uterine activity in response to buccal Pitocin. Since the uterine response does not depend only on the level of oxytocin in the blood, but also on the sensitivity of the myometrium to oxytocin, neither buccal nor intravenous administration precludes overstimulation of the uterus. If hyperstimulation does occur, the longer half-life with buccal Pitocin is a disadvantage.

### REFERENCES

- 1. Theobald, G. W.: The neurohypophysis and labour, in Philip, E. E., Barnes, J., and Newton, M., editors: Scientific Foundations of Obstetrics and Gynecology, London, 1970, William Heinemann, Ltd.
- Turnbull, A. C., and Anderson, A. B. M.: Induction of labour. Part 2. Intravenous oxytocin infusion, J. Obstet. Gynaecol. Br. Commonw. 75:24, 1968.
- 3. Dawood, M. Y., Raghavan, K. S., and Pociask, C.: Radioimmunoassay of oxytocin, J. Endocrinol. 76:261, 1978.
- Dawood, M. Y., Raghavan, K. S., Pociask, C., and Fuchs, F.: Oxytocin in human pregnancy and parturition, Obstet. Gynecol. 51:138, 1978.
- duVigneaud, V., Ressler, C., Swan, J. M., Roberts, C. W., Katsoyannis, P. G., and Gordon, S.: The synthesis of an octapeptide amide with the hormonal activity oxytocin, J. Am. Chem. Soc. 75:4879, 1954.
- Dillon, T. F., Douglas, R. G., duVigneaud, V., and Barber, H. L.: Transbuccal administration of Pitocin for induction and stimulation of labor, Obstet. Gynecol. 15:587, 1960.
- Newman, J. W., and Hon, E. H.: Induction of labor with transbuccal oxytocin, Obstet. Gynecol. 21:3, 1963.

- Noriega-Guerra, L., Aznar, R., Arevalo, N., Martinez-Zalce, G., del Campo, E. M., and Lepe, C. M.: Disadvantages of administration of oxytocin by oral absorption, Am. J. Obstet. Gynecol. 96:849, 1966.
- Dawood M. Y., Ylikorkala, O., Trivedi, D., and Fuchs, F.: Oxytocin in maternal circulation and amniotic fluid during pregnancy, J. Clin. Endocrinol. Metab. 49:429, 1979.
- 10. Fabian, M., Forsling, M. L., Jones, J. J., and Pryor, J. S.: The clearance and antidiuretic potency of neurohypophysial hormones in man, and their plasma binding and stability, J. Physiol. (Lond.) 204:653, 1969.
- stability, J. Physiol. (Lond.) 204:653, 1969.

  11. Chard, T., Boyd, N. R. H., Forsling, M. L., McNeilly, A. S., and Landon J.: The development of a radioimmunoassay for oxytocin, the extraction of oxytocin from plasma and its measurement during parturition in human and goat blood. J. Endocrinol. 48:223, 1970.
- Dawood, M. Y., Ylikorkala, O., Trivedi, D., and Gupta, R.: The effect of oxytocin infusion on plasma FSH, LH, oxytocin and its clearance in adult males, J. Clin. Endocrinol. Metab. 50:397, 1980.

## Analysis of amniotic fluid, maternal plasma, and cord blood for a human breast gross cystic disease fluid protein

DARROW E. HAAGENSEN, JR., M.D., PH.D. STANLEY A. GALL, M.D. JANE E. BRAZY, M.D. JAN GIANNOLA, R.N. SAMUEL A. WELLS, JR., M.D. Durham, North Carolina

Amniotic fluid was analyzed for the presence of the 15,000 monomer molecular size glycoprotein found in human breast gross cystic disease fluid (GCDFP-15). From 24 weeks' gestation a log-linear increase in levels of GCDFP-15 was noted. The levels of GCDFP-15 doubled every 16 to 28 days, and the highest value recorded was 7,200 ng/ml. At delivery, levels of GCDFP-15 in cord blood plasma were in a background range (mean, 8 ng/ml). Maternal plasma levels of GCDFP-15 were one to tenfold higher in the third trimester of pregnancy when compared to those in nonpregnant women. Since saliva is known to contain high concentrations of GCDFP-15 (10 to 70  $\mu$ g/ml), it is proposed that the levels in amnictic fluid originate from saliva and tracheobronchial secretions. (Am. J. Obstet. Gynecol. 138:25, 1980.)

AMNIOTIC FLUID has been analyzed to ascertain a variety of parameters of fetal-maternal well-being and development. The lecithin-sphingomyelin (L/S) ratio is a reasonably accurate indicator of fetal lung maturity and helps to predict the likelihood of respiratory distress syndrome (RDS) in the delivered neonates. <sup>1–6</sup>

Amniotic fluid appears to be generated from several sources. It is a selective transudate of maternal plasma to which is added fetal plasma transudate, fetal urine, and fetal orotracheal secretions. At approximately 20 weeks' gestation, the volume of amniotic fluid is around 350 ml. Skin keratinization of the fetus occurs from 24 to 26 weeks, and this event decreases fetal plasma transudate. The maximum volume of amniotic fluid is obtained around 38 weeks' gestation and averages approximately 1,000 ml. With increasing gestational age, an increasing proportion of amniotic fluid is

From the Departments of Surgery, Pediatrics, and Obstetrics and Gynecology, Duke University Medical Center.

Received for publication September 17, 1979.

Revised March 25, 1980. Accepted April 8, 1980.

Reprint requests: Dr. Darrow E. Haagensen, Jr., The Mallory Institute of Pathology, 784 Massachusetts Ave., Boston, Massachusetts 02118.

accounted for by fetal urine and fetal orotracheal secretions. A concomitant decrease in the total protein content of amniotic fluid occurs with increasing gestational age, reaching approximately one twentieth of the normal serum protein content at term. The water exchange between fetus and mother has been calculated to be from 500 to 3,000 ml per hour at term. The water is reached, the amniotic fluid becomes hypotonic because of the increased contribution of fetal urine, as evidenced by the increasing urea and creatinine content.

The analysis of human breast gross cystic disease fluid has demonstrated several unique glycoproteins.13 One of these proteins (GCDFP-15) monomer size 15,000, has been demonstrated to be immunclogically identical to a component of human saliva. The GCDFP-15 is present in gross cystic disease (GCD) fluid at approximately a 100-fold higher concentration than in saliva (1 to 10 mg/ml in GCD fluid versus 10 to 70  $\mu$ g/ml in saliva). By radioimmunoassay, the GCDFP-15 component is present in "normal" human adult plasma at a level of 5 to 85 ng/ml. For patients with metastatic breast carcinoma, plasma levels of GCDFP-15 above 150 ng/ml have been found (range, 150 to 40,000 ng/ml).14 In this article, we report on the levels of. GCDFP-15 in maternal plasma, fetal plasma, and amniotic fluid, and relate these levels to fetal maturation.

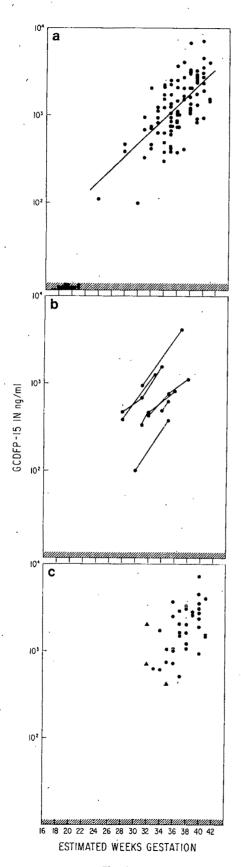


Fig. 1

### Material and methods

Amniocentesis after 20 weeks' gestation was strictly for maternal and/or fetal indications. Amniotic fluid obtained prior to 20 weeks' gestation was collected at the time of amniocentesis for genetic counseling or for abortion. A 500- $\mu$ l aliquot of each sample of amniotic fluid was centrifuged at 1,000 × g for 5 minutes, and the supernatant was decanted and stored at -70° C until time of analysis. No antibacterial agents were added.

For correlation purposes, information was obtained on possible maternal problems (RH sensitization, pre-eclampsia, diabetes, rupture of membranes) and on possible fetal/neonatal problems (Apgar score, L/S ratio, respiratory distress syndrome, congenital anomalies, birth weight, gestational age, erythroblastosis).

At the time of birth, samples of cord blood from the placental side were collected into K3-EDTA tubes for analysis. Samples of maternal blood were obtained during various stages of gestation from women visiting the prepartum clinic at Duke University Medical Center. Some of these women underwent amniocentesis for therapeutic indications, as stated above. Samples of blood were processed to plasma by centrifugation, 20 minutes at 2,000 rpm, and the plasma was stored at  $-70^{\circ}$  C until analysis.

The analysis of the GCDFP-15 content in plasma, cord blood, and amniotic fluid was approved at Duke University Medical Center by the Experimental Investigations Committee and by the Investigations Committee of the Department of Obstetrics and Gynecology. The L/S ratio of samples of amniotic fluid was determined as a routine assay, according to the procedure of Gluck and associates.<sup>2</sup>

The GCDFP-15 content of collected samples was analyzed by radioimmunoassay. Samples of plasma (50- $\mu$ l aliquots) in duplicate were tested as described previously. For analysis of amniotic fluid, the GCDFP-15 radioimmunoassay was performed in an isotope dilution mode wherein sample, radioactive tracer, and specific antibody were all added at the same time. The assay tubes were incubated overnight at room temperature, and then the specific antibody binding to tracer was determined by precipitation with a goat-anti-rabbit antibody attached to a solid-phase bead of vinylidine fluoride (Kynar). The procedure for this assay was as

Fig. 1. Depicted are levels of GCDFP-15 in amniotic fluid versus estimated weeks' gestation. In a are 115 separate samples from 16 to 42 weeks' gestation. The tangential line is the least-squares regression line for the 95 values above the assay background (shaded area). In b are serial samples from seven patients. In c are 38 samples obtained within 72 hours of delivery. The three  $\triangle$  represent neonatal deaths.

1.

**Table I.** GCDFP-15 levels for 38 samples of amniotic fluid obtained within 72 hours of delivery

GCDFP-15 (ng/ml)	L/S ratio	Estimated weeks' gestation	Birth weight (grams)	Apgar score (1 min/5 min)	Complications
405	2.4	37	2,140	9/10	Twins, birth weights below 2,500 grams
			2,460	7/9	
423	•	- 35	1,820		Anencephalic (stillborn)
610	2.2	34	2,350	8/9	Premature rupture of membranes
630	3.1	33	2,260	6/4	Respiratory distress syndrome, survived
720	2.1	32	740	8/7	Respiratory distress syndrome, died of hyaline membrane disease
735	1.2	35	2,780	8/9	Rh sensitized
780	6.1	35	3,090	8/9	Maternal diabetes, pre-eclampsia
1,005	2.2	· 36	2,400	9/10	Birth weight below 2,500 grams
1,015		36	2,800	7/7	Fetal distress in delivery
1,060	3.6	35	1,970	9/9	Premature labor-low birth weight
1,485	4.3	41	2,990	9/9	Sickle cell (+) Hg-AS
1,710	3.7	34	2,330	8/9	Premature labor—low birth weight, severe fetal decelerations
2,050	0.7	32	3,235	I/1	Congenital lung anomalies of multiple cystic adenomatosis
2,970	2.3	37	2,140	9/9	Birth weight below 2,500 grams
>900	>2.0	>35	>2,500	>7/7	24 births without neonatal problems

follows: 5-ml polypropylene tubes were used as the reaction vessels; added at the same time by automatic pipetter (Prias, Packard) to each tube was 50 µl of test sample; 100 µl of 125I-GCDFP-15 radioactive tracer (approximately 5 ng and 40,000 to 80,000 counts per minute, depending on age of tracer); 100 µl of a 1:2,000 dilution of specific rabbit antibody against the GCDFP-15; and 1 ml of 0.1M ammonium acetate buffer, pH 7, containing 1 mg/ml of bovine albumin (ammonium acetate-albumin buffer). A six-point inhibition curve was generated with the use of  $0 \mu l$ ,  $100 \mu l$ , 200  $\mu$ l, 300  $\mu$ l, 400  $\mu$ l, and 500  $\mu$ l of the GCDFP-15 standard (50 ng/ml in ammonium acetate-albumin buffer), which was equivalent to 0 ng, 5 ng, 10 ng, 15 ng, 20 ng, and 25 ng of the GCDFP-15. The assay volume for the standard tubes was kept constant and equal to that for the experimental tubes by bringing the total assay tube volume to 1.25 ml with ammonium acetate-albumin buffer. All assay tubes were incubated at room temperature overnight. The reaction was terminated by the addition of 0.5 ml goat-anti-rabbit antibody attached to Kynar (gift of Dr. Hans I. Hansen, Hoffmann LaRoche). The Kynar-attached second antibody was able to bind between 5 and 10  $\mu$ g of IgG permilliliter of a 2% suspension. Antibody precipitation was complete within 30 minutes, after which the assay tubes were centrifuged at 3,000 rpm for 5 minutes, the supernatant was decanted, and the pellet was counted in a Packard gamma scintillation counter (Prias) with the counting efficiency of approximately 70%.

The 125I-GCDFP-15 control tubes (no antibody against GCDFP-15 being present) had 12% of the counts precipitated by the Kynar-bound second antibody. The

zero point of the antibody inhibition curve was set at 60% of added counts being precipitated. The addition of an increasing quantity of cold GCDFP-15 to 25 ng caused a decrease in counts precipitated from 60% to 20%. The limit of sensitivity for this assay was 0.5 ng per 50-µl sample. Duplicate point values were maintained within ±2% of each other. The samples of amniotic fluid were analyzed in duplicate as 50-µl aliquots undiluted and diluted 1 to 5 in ammonium acetatealbumin buffer in order to include an antigen range from 0 to 2,500 ng GCDFP-15 per milliliter sample on initial analysis. Further dilution of samples for analysis was carried out with ammonium acetate-albumin buffer if the above scale was not sufficient for the GCDFP-15 level.

Sephadex G-200 column chromatography was performed on a column 2.6 by 90 cm at 10° C. Ammonium acetate buffer, pH 7.0, 0.1M, was used as the eluent with an elution rate of 16 ml per hour by gravity flow. Absorbance of eluent fractions (4.5 ml each) was determined at 280 nm (Coleman 46 Spectrophotometer). Molecular size of eluted material was judged relative to human albumin as a standard. The GCDFP-15 content of eluted fractions was determined by radioimmunoassay of aliquots from each 4.5-ml fraction.

### Results

A total of 115 samples of amniotic fluid was obtained from 103 pregnant women. Twenty of the samples ... were from 20 women who were undergoing secondtrimester abortions (16 to 21 weeks' gestation). Fiftyfour samples were from 44 women who were evaluated between 24 and 36 weeks' gestation, and 41 samples ..

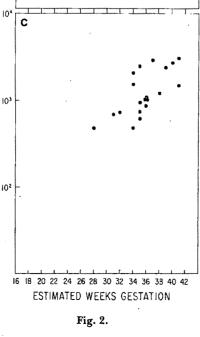


Table II. Amniotic fluids with L/S ratios below 2.0

L/S ratio	GCDFP-15 (ng/ml)	Estimated weeks' gestation	Complications
0.3	389 -	28	Maternal Rh negative
0.7	1,255	33	Maternal Rh negative
0.7	2,050	32	Congenital lung anomalies
8.0	740	32	None
0.9	468	28	Maternal hypertension
0.9	690	31	Maternal hypertension
1.1	1,305	39	Maternal diabetes, Class A
1.2	710	33	None
1.3	335	31	Maternal Rh negative
1.3	465	32	Maternal Rh negative
1.3	377	35	Maternal Rh negative
1.3	490	34	Maternal hypertension
1.6	605	35	Maternal hypertension
1.6	1,100	38	Maternal Rh negative
1.6	2,300	35	Maternal Rh negative
1.7	955	31	Maternal Rh negative
1.7	1,215	34	None
1.9	1,170	38	None
1.9	1,290	35	None
1.9	2,550	35	Pre-eclampsia
1.9	2,325	34	Maternal Rh negative

were from 39 women who were between 37 and 42 weeks' gestation. Thirty-eight of the samples of amniotic fluid were obtained during the 72 hours prior to delivery.

Fig. 1, a depicts the relationship of levels of GCDFP-15 in amniotic fluid to weeks of gestation. The 20 samples of amniotic fluid of less than 22 weeks' gestational age had GCDFP-15 levels of <20 ng/ml. The first gestationally positive amniotic fluid GCDFP-15 level (113 ng/ml) was detected at 24 weeks' gestation. The highest amniotic fluid GCDFP-15 level encountered (7,200 ng/ml) was from a 40-week-gestation sample. A least-squares regression line analysis of the positive GCDFP-15 levels indicated an apparent log-linear increase of GCDFP-15 with increasing age of gestation (R = 0.68, p = < 0.00001).

Fig. 1, b depicts the levels of GCDFP-15 in serial samples of amniotic fluid from seven patients. Each of the serial samples demonstrated increasing levels of GCDFP-15 with increasing gestational age. This increase appeared to be log-linear, with a doubling time of approximately 16 to 28 days.

Thirty-eight amniotic fluid GCDFP-15 levels were obtained within 72 hours of delivery (Fig. 1, c). They

Fig. 2. Depicted are levels of GCDFP-15 in amniotic fluid versus estimated weeks' gestation. In a are 40 samples from diabetic mothers. The letters represent the stage of diabetes (A to F). In b are 27 samples from mothers who were Rh negative and sensitized. In c are 20 samples from mothers with hypertension.

Table III. Amniotic fluids with L/S ratios >2.0 and GCDFP-15 levels <900 ng/ml

		G	
GCDFP-15 (ng/ml)	L/S ratio	Estimated weeks' gestation	Complications
300	2.5	34	Maternal diabetes, Class C
374	2.0	36	Maternal diabetes, Class C
385	2.1	33	Maternal diabetes, Class F
405	2.4	37	Twins
438	3.6	35	None
610	2.2	34	Premature rupture of membranes
630	3.1	33	Maternal diabetes, Class D, neonatal respiratory dis- tress syndrome
720	2.1	32	Neonatal respira- tory distress syndrome
760	6.1	35	Maternal diabetes, Class A
840	2.5	36	Maternal diabetes, Class A
840	2.3	39	Maternal diabetes, Class A

Table IV. Maternal plasma levels of GCDFP-15 versus estimated weeks of gestation

	Weeks of gestation		
GCDFP-15 (ng/ml)	0 to 23	24 to 36	37 to 42
100	36 (84 %)	30 (43%)	13 (19%)
100-150	7 (16%)	22 (31%)	18 (26%)
150	0 (0%)	18 (26%)	37 (55%)
Totals	43	70	68

are stratified in Table I in relation to level of GCDFP-15, L/S ratio, estimated weeks' geatation, birth weight, Apgar score, and complications. Of the three neonatal deaths which occurred, the GCDFP-15 amniotic fluid level was below 900 ng/ml in two, being 423 ng/ml in the anencephalic case, and 720 ng/ml in the case of death due to RDS with hyaline membrane disease. The neonate who died with severe congenital lung anomalies had a GCDFP-15 amniotic fluid level of 2,050 ng/ml.

Of 115 samples of amniotic fluid collected, 20 from patients with gestational ages less than 22 weeks were not subjected to the determination of L/S ratios. Of the other 95 samples, 79 L/S ratios were obtained. In 21 of the 79 samples, the L/S ratios were below 2, with 12 of the values being below 1.5. The 20 samples with L/S below 2.0 are compared in Table II with the GCDFP-15 levels, the week of gestation, and complicating problems. Of these 21 samples, two were obtained at 28

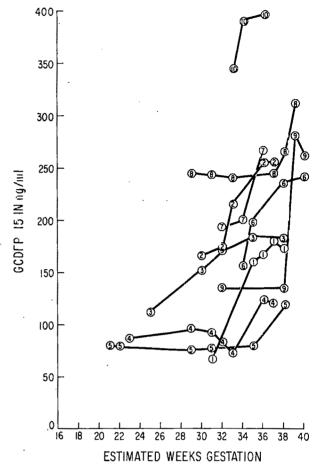


Fig. 3. Depicted are the serial maternal plasma levels of GCDFP-15 in 10 patients versus estimated weeks' gestation.

weeks' gestation, 16 were obtained between 31 and 35 weeks' gestation, and three were obtained between 38 and 39 weeks' gestation. The amniotic fluid GCDFP-15 levels were below 900 ng/ml in both 28-week-gestation samples (389 ng/ml and 468 ng/ml). Eight of the 16 samples between 31 and 35 weeks had GCDFP-15 levels below 900 ng/ml. All three of the samples of amniotic fluid of 38 to 39 weeks' gestation had GCDFP-15 levels above 900 ng/ml.

Of the 58 samples of amniotic fluid with L/S ratios which were above 2, eleven had GCDFP-15 levels below 900 ng/ml. These eleven GCDFP-15 levels are compared in Table III with the L/S ratio, the estimated weeks' gestation, and neonatal or maternal complications. It is of interest that samples of amniotic fluid from four pregnant women with advanced diabetes (Classes C, D, and F) had mature L/S ratios with low levels of GCDFP-15 levels.

Within the group of 95 samples of amniotic fluid collected from patients of 24 weeks' gestation to termwere 40 samples from women with diabetes mellitus.

**Table V.** Comparison of prepartum and early postpartum plasma levels of GCDFP-15

Prepartum GCDFP-15 (ng/ml)	Postpartum day of plasma sample	Postpartum GCDFP-15 (ng/ml
220	l day	200
248	l day	220
312	l day	260
284	2 day	400
276	2 day	250
308	2 day	192
316	2 day	384

Table VI. GCDFP-15 plasma levels in seven women between 4 and 16 weeks post partum

Week post partum	Nursing	Plasma GCDFP-15 (ng/ml)	
4	Yes	68	
6	No	120	
6	Yes	123	
7	Yes	40	
10	No	12	
10	No	36	
16	Yes	38	

The range of GCDFP-15 levels in diabetic patients was within the overall range for the other samples of amniotic fluid (Fig. 2, a).

Contained in the pool of 95 samples of amniotic fluid were 20 samples from pregnant women with preeclampsia, and 27 samples from pregnant women who were Rh sensitized. These 47 samples were within the overall range for the other samples of amniotic fluid (Fig. 2, b and c).

Concomitant with the analysis of samples of amniotic fluid for GCDFP-15 levels has been the analysis of 164 samples of cord blood obtained from the placental side at the time of birth and the analysis of 375 samples of plasma from 181 prepartum women. Twenty-four of the prepartum samples of plasma were from 19 women who underwent amniotcentesis. Twenty-one samples of plasma from 20 postpartum women were also obtained for analysis.

Among the 164 samples of cord blood, there were 155 GCDFP-15 plasma levels below 30 ng/ml, with a range of 0 to 28 ng/ml and a mean value of 8 ng/ml. On the other nine samples, the GCDFP-15 levels ranged from 48 to 110 ng/ml. No differences were noticed for the nine neonates with GCDFP-15 cord blood levels between 48 and 110 ng/ml as compared to the 155 neonates with the lower GCDFP-15 cord blood levels. It is apparent from these data that the GCDFP-15 levels which are uniformly elevated in amniotic fluid at term are not reflected in the fetal cord blood.

The plasma levels of GCDFP-15 in 92 nonpregnant,

normal women, who ranged in age between 24 and 72 years, varied from 7 to 81 ng/ml (mean, 31 ng/ml).14 In 252 nonpregnant women with a variety of benign breast diseases, the GCDFP-15 plasma levels were all below L50 ng/ml. The only patients with benign breast disease who had GCDFP-15 plasma levels between 100 and 150 ng/ml were women with gross cystic disease of the breast.14

The 181 pregnant women for whom plasma levels of GCDFP-15 were determined were divided for analysis into gestational age categories in a manner similar to that for analysis of samples of amniotic fluid (Table IV). Only a proportion of women of more than 24 weeks' gestation had GCDFP-15 plasma levels above 150 ng'ml (26% of those between 24 and 36 weeks and 55% for 37 weeks to term). The highest GCDFP-15 plasma level observed in a pregnant woman was 396 ng/ml at 35 weeks' gestation.

Serial plasma levels of GCDFP-15 were obtained in 55 of the 181 pregnant women. The GCDFP-15 plasma levels increased with increasing age of gestation; however, the degree of increase was variable, as was the time course of increase. As parturition neared, a significant increase in the levels of GCDFP-15 was observed in some pregnant women and not in others. Plasma levels for 10 of the pregnant women for whom there vere serial samples are plotted in Fig. 3. These patients are representative of the changing plasma levels of GCDFP-15 observed with increasing age of gestation.

Among 14 plasma samples from patients 1 to 2 days post partum, 12 had GCDFP-15 levels above 150 ng/ml In seven of these patients, samples of plasma within 48 hours prior to delivery were compared and found to be similar (Table V).

Seven patients evaluated between 4 weeks and 16 weeks after parturition had GCDFP-15 levels below 150 rg/ml; five of the seven values were below 100 ng/ml (Table VI).

The amniotic fluid GCDFP-15 was identical with the GCDTP-15 antigen standard isolated from breast GCD fluid, as judged by parallel competitive inhibition capacity for various dilutions of amniotic fluid samples versu; the GCDFP-15 standard (Fig. 4). Of interest, therefore, was the molecular size of the amniotic fluid GCDFP-15 analogue in comparison to the human breas: GCDFP-15 component. Sephadex G-200 chromatography of a sample of amniotic fluid containing 4  $\mu g$  of GCDFP-15 gave an elution profile which was similar to 5  $\mu$ g of the GCDFP-15 antigen standard (Fig. 5). The GCDFP-15 component profile was determined by inhibitory activity on radioimmunoassay. An albumin solution was used as the molecular size reference protein on each column analysis. The estimation of molecular size of GCDFP-15 on column chromatography (40,000 daltons) is aberrant relative to the monomer molecular size because of polymer formation.<sup>13</sup> The GCDFP-15 activity in amniotic fluid had an estimated molecular size of 47,000 daltons, which also may indicate a polymeric form of the molecule.

### Comment

Analysis of amniotic fluid for GCDFP-15 has demonstrated a range of levels which appear to correlate with gestational age (Fig. 1, a). The GCDFP-15 levels began to increase at approximately 24 weeks' gestation. Analysis of serial samples of amniotic fluid indicated a log-linear doubling of GCDFP-15 toward term, with a doubling time of 16 to 28 days (Fig. 1, b). The GCDFP-15 content of all samples of amniotic fluid versus weeks' gestation also indicated a log-linear relationship with a mean doubling time of approximately 28 days (Fig. 1, a).

Analysis of GCDFP-15 levels in amniotic fluid relative to other known variables of fetal maturation (L/S ratio, gestational age, birth weight) indicated that the amniotic fluid GCDFP-15 levels were sensing an aspect of fetal maturation not precisely related to the abovementioned three variables. There was an indication of relatively lower GCDFP-15 levels in amniotic fluid whenever fetal maturation was slow or abnormal (Table I), or whenever fetal-maternal problems existed (Tables I, II, and III).

In the cases of advanced maternal diabetes (Classes D-F), in which the L/S ratio may mature early, relatively lower GCDFP-15 levels were observed (Table III). However, for conditions in which the L/S ratio maturation may be retarded (Rh incompatibility and maternal diabetes Classes A and B), approximately 50% of the GCDFP-15 levels were above 900 ng/ml at a time when the L/S ratio was below 2 (Table II). It is apparent from this analysis that elevating GCDFP-15 levels in amniotic fluid are monitoring a parameter of fetal development not monitored by the L/S ratio, and the GCDFP-15 levels are affected differently from the L/S ratio by conditions which influence fetal-maternal well-being and compatibility (diabetes, Rh).

It is of interest to speculate about the source of the GCDFP-15 in amniotic fluid. Previous studies have indicated that the GCDFP-15 molecule has an apocrine cell predominance in body location. 15 The molecule is found in relatively high levels in axillary sweat glands, anal sweat glands, saliva, and human milk. It is also present in the abnormal secretion of human breast gross cystic disease fluid and in human breast carcinoma cells. During fetal maturation, the cough reflex,

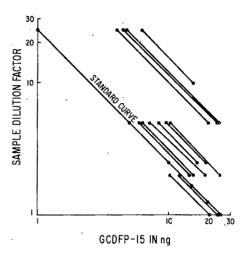


Fig. 4. Depicted on a log-log scale are amniotic fluid serial dilution GCDFP-15 values for 12 separate samples. Each sample paralleled the standard curve.

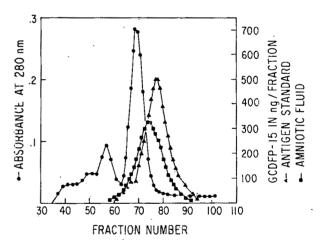


Fig. 5. Depicted are two separate G-200 column analyses of molecular size. The albumin elution peaks have been overlaid for comparative analysis of profile. The first column had 1 ml cf amniotic fluid (containing approximately 4 µg GCDFP-15 activity) mixed with 30 mg of crystallized human albumin for column application. The second column had 5  $\mu$ g of purified GCDFP-15 mixed with 30 mg of crystallized human albumin in a total volume of 1 ml for column application. The GCDFP-15 content was determined by radioimmunoassay for amniotic fluid (■), and the purified sample (▲). Optical density of the albumin peak was determined at 280 nanometers (•).

which produces saliva and tracheobronchial fluid, may account for a significant part of the level of GCDFP-15 in amniotic fluid. Previous analysis of placenta tissue15 has indicated that this tissue does not contain any significant quantity of GCDFP-15. Skin keratinization apparently occurs at about 24 weeks' gestation. If apocrine sweat glands are active in utero, they could be a source of GCDFP-15; however, in general, sweat glands are not considered to be active in utero.

The analysis of urine from patients with metastatic breast carcinoma has indicated that the GCDFP-15 in plasma is predominantly cleared by urinary excretion (unpublished observations). Thus, it is quite possible that any circulating fetal plasma GCDFP-15 would accumulate in amniotic fluid because of urinary excretion. However, the analysis of fetal cord blood indicated minuscule levels of GCDFP-15 in fetal plasma compared to the GCDFP-15 content in term amniotic fluid.

Although it is possible that the GCDFP-15 in amniotic fluid represents a maternal contribution, this would require a selective enhancing capacity of the placenta, since the amniotic fluid levels on an equal-volume basis are several-fold higher than maternal plasma levels. More likely is the possibility that maternal GCDFP-15 levels are secondary to elevations of amniotic fluid GCDFP-15. In favor of this observation is the decrease in maternal GCDFP-15 which occurs post partum (Tables V and VI).

Since the breast is a known source of GCDFP-15, the

maternal plasma levels of GCDFP-15 in nursing versus nonnursing mothers was of interest. No significant difference in plasma levels was present for these two categories of women (Table VI).

By competitive inhibition analysis on radioimmuno-assay (Fig. 4) and by Sephadex G-200 chromatography (Fig. 5], the amniotic fluid GCDFP-15 was quite similar to the GCDFP-15 molecule isolated from human breast gross cystic disease fluid.

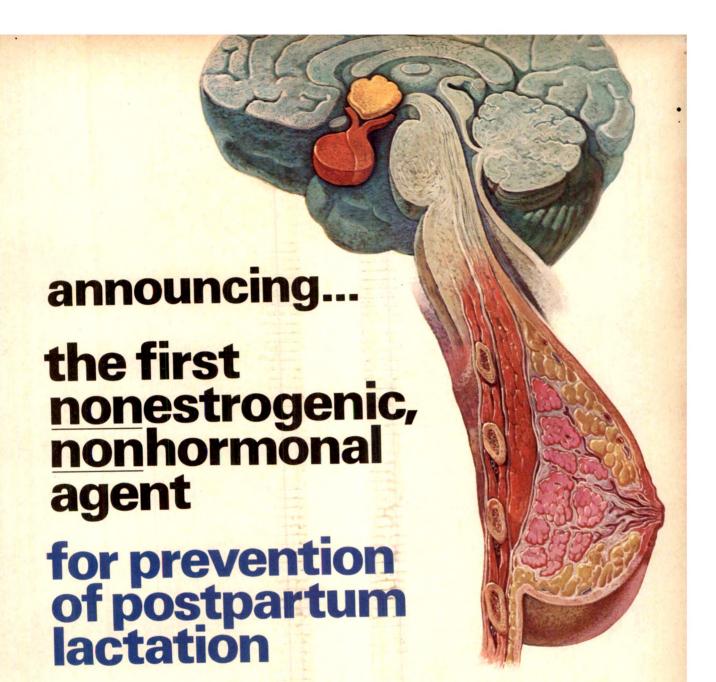
Our data indicate that the GCDFP-15 content of amnio ic fluid correlates with a parameter of fetal maturation. Although the cough-regurgitant reflex that produces saliva is the most likely fetal source of the GCDFP-15, further studies are required to determine more precisely the relative contribution of other potential sources of GCDFP-15, as discussed above. The clinical usefulness of the measurement of amniotic fluid GCDFP-15 will depend on a precise definition of the source of GCDFP-15 and determination of how this aspect of fetal maturation is related to other aspects of fetal cevelopment and well-being.

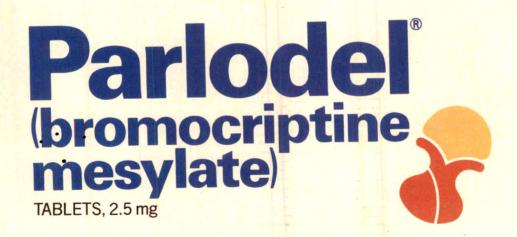
### REFERENCES

- Gluck, L., and Kulovich, M. V.: Lecithin/sphingomyelin ratios in amniotic fluid in normal and abnormal pregnancy, Am. J. OBSTET. GYNECOL. 115:539, 1973.
- Gluck, L., Kulovich, M. V., Borer, R. B., Jr., and Keidel, W. N.: The interpretation and significance of the lecithin/ sphingomyelin ratio in amniotic fluid, Am. J. Obstet. Gynecol. 120:142, 1974.
- Johnson, L. W.: Determining fetal lung maturity: A sensitive surfactant method, Am. J. OBSTET. GYNECOL. 129:190, 1977.
- Hallman, M., Kulovich, M., Kirkpatrick, E., Sugarman, R. G., and Gluck, L.: Phosphatidylinositol and phosphatidylglycerol in amniotic fluid: Indices of lung maturity, Am. J. Obstet. Gynecol. 125:613, 1976.
- Donald, I. R., Freeman, R. K., Goebelsmann, U., Chan, W. H., and Nakamura, R. M.: Clinical experience with the amniotic fluid lecithin/sphingomyelin ratio, Am. J. OBSTET. GYNECOL. 115:547, 1973.
- 6. Gabbe, S. G., Lowensohn, R. I., Mestman, J. H., Freeman, R. K., and Goebelsmann, U.: Lecithin/sphingomyelin ratio in pregnancies complicated by diabetes mellitus, Am. J. Obstet. Gynecol. 128:757, 1977.
- Queenan, J. T., Gadow, E. C., Bachner, P., and Kubarych, S. F.: Amniotic fluid proteins in normal and Rheensitized pregnancies, Am. J. Obstet. Gynecol. 108: 406, 1970.
- 8. Jonasson, L.-E.: Total protein content in amniotic fluid from normal pregnancies and from pregnancies complicated by Rh-isoimmunization, Acta Obstet. Gynecol. Scand. 51:187, 1972.

- 9. Queenan, J. T., Thompson, W., Whitfield, C. R., and Shah, S. I.: Amniotic fluid volumes in normal pregnancies, Am. J. Obstet. Gynecol. 114:34, 1972.
- Gidin, D., Kumate, J., Morales, C., Noriega, L., and Aravalo, N.: The turnover of amniotic fluid protein in the human conceptus, Am. J. Obstet. Gynecol. 113:632, 1972.
- 11. Hatchinson, D. Z., Hunter, C. B., Neslen, E. D., and Plentl, A. A.: The exchange of water and electrolytes in the mechanism of amniotic fluid formation and the relationship to hydramnios, Surg. Gynecol. Obstet. 100:391, 1⊆55.
- 12. Hatchinson, D. L., Gray, M. J., Plentl, A. A., Alvarez, H., Caldeyro-Barcia, R., Kaplan, B., and Lind, J.: The role of the fetus in the water exchange of the amniotic fluid of normal and hydramniotic patients, J. Clin. Invest. 38:971, 1959.
- 13. Haagensen, D. E., Jr., Mazoujian, G., Dilley, W. G., Pedersen, C. E., Kister, S. J., and Wells, S. A., Jr.: Breast gross cystic disease fluid analysis. I. Isolation and radio-inamunoassay for a major component protein, J. Natl. Cancer Inst. 62:239, 1979.
- 14. Haagensen, D. E., Jr., Mazoujian, G., Holder, W. D., Jr., Kister, S. J., and Wells, S. A., Jr.: Evaluation of a breast crst fluid protein detectable in the plasma of breast carcinoma patients. Ann. Surg. 185:279, 1977.
- noma patients, Ann. Surg. 185:279, 1977.

  15. Haagensen, D. E., Jr., and Wells, S. A., Jr.: Plasma human breast gross cystic disease fluid assay, in Herberman, R. B., editor: Compendium of Assays for Immunodiagnosis of Human Cancer, New York, 1979, Elsevier-North Holland Publishing Company, p. 397.



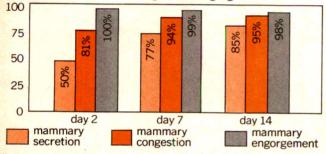


## The need for an alternative to estrogens and other hormones in the prevention of postpartum lactation is met with Parlodel bromocriptine mesylate

### Extremely high clinical response, based on complete absence—not just relief—of mammary secretion, congestion, and engorgement

By day 14 of Parlodel therapy,\* 85% of the patients who completed at least 14 days of therapy had complete absence of secretion, and all but two of these women achieved this response by day 12; in the remaining 15%, secretion was rated as slight to moderate. By day 7, 94% of the patients had complete absence of congestion, and this remained essentially unchanged through day 14. Furthermore, 98% had complete absence of engorgement; significantly, few patients developed engorgement at any time during therapy—never over 9%.

Percent of patients reporting complete absence of mammary secretion, congestion, engorgement\*



\*Based on 70 patients who completed at least 7 days of therapy and 66 patients who completed at least 14 days of therapy. Half of each group received 5.0 mg a day and the other half received 7.5 mg a day, in divided doses.

It should be kept in mind that the incidence of significant painful engorgement is low and usually responsive to appropriate supportive therapy. In contrast

with supportive therapy, Parlodel (bromocriptine mesylate) prevents the secretion of prolactin, thus inhibiting lactogenesis and subsequent secretion. congestion, and engorgement.

In other studies 1,2 with Parlodel therapy it was noted that there "were no complaints of engorged or painful breasts..." and that "... the almost complete relief of pain and engorgement spared both the patient and the nursing staff many complaints, and justified the longer duration of treatment."2

Mild to moderate secretion, congestion, or engorgement occurs in 18% to 40% of patients once therapy

### High correlation between clinical response and reduction of prolactin levels demonstrated<sup>3</sup>

In nine postpartum patients Parlodel therapy was initiated after delivery. Five hours after the first Parlodel dose, serum prolactin levels had fallen to the normal range and, over the eight days they were measured, remained below an estimated mean normal. Prolactin concentrations did not rise even following nipple stimulation in the five patients tested in this manner. None of the nine patients had any milk secretion or breast engorgement.

### No effect on clotting factors 4.5

Adverse reactions were generally mild to moderate and required discontinuation of therapy in only 3% of 234 patients treated with 2.5 mg to 7.5 mg daily for prevention of postpartum lactation. Headache, dizziness, nausea, and hypotension were among the side effects observed. (See Brief Summary.)

### Recommended dosage and administration in prevention of postpartum lactation

 one 2.5-mg tablet bid with meals for 14 days (if necessary, may be given for up to 21 days); since Parlodel (bromocriptine mesylate) is known to cause hypotension in some patients, therapy should be started only after vital signs have been stabilized and no sooner than four hours after delivery

1. Rolland R, De Jong FH, Schellekens LA, Lequin RM: The role of prolactin in the restoration of ovarian function during the early post-partum period in the human femate: II. A study during inhibition of lactation by bromergocryptine. Clin Endocrinol 4:27-38. 1975. 2. Rolland R, Schellekens L: A new approach to the inhibition of puerperal lactation. Br J Obstel Gynaecol. 80 945-951. 1973. 3. Brun del Re R, del Pozo E, de Grandi P, et al. Prolactin inhibition and suppression of puerperal lactation by a Br-ergocryptine (CB 154): A comparison with estrogen. Obstel Gynaecol. 41:884-890, 1973. 4. Nilsen PA. Meling AB. Abildgaard U. Study of the suppression of lactation and the influence or blood clotting with bromocriptine (CB 154) (Partoder!"). A double blind comparison with diethylstilboort. Acta Obstel Gynaecol Scand 55:39-44, 1976. 5. Cooke I; holey M, Lenton E, et al. The treatment of puerperal lactation with boomocriptine. Postgrad Med J 52(suppl 1):75-80, 1976.

Indications: Short-term treatment of amenorrhea/galactorrhea associated with hyperprolactinemia due to varied etiologies, excluding demonstrable pituitary tumors: not indicated in patients with normal prolactin levels, and, since safe use has not been demonstrated in pregnancy, not indicated in management of infertility

Prevention of physiological lactation, (secretion, congestion, and engorgement) after parturition, when the mother elects not to breast feed or breast feeding is contraindicated, or after stillbirth or abortion. The physician should keep in mind that the incidence of significant painful engorgement is low and usually responsive to appropriate supportive therapy. In contrast with supportive therapy, Parlodel® (bromocriptine mesylate) prevents the secretion of prolactin, thus inhibiting lactogenesis and subsequent

secretion, congestion, and engorgement. Once Parlodel therapy is stopped, 18% to 40% of patients experience rebound of breast secretion, congestion, or engorgement, which is usually mild to moderate in severity.

Contraindications: Sensitivity to any ergot alkaloids.

Warnings: Since hyperprolactinemia with amenorrhea/galactorrhea has been found in patients with pituitary tumors (Forbes-Albright syndrome), a complete evaluation of the sella turcica is advisable before treatment with Parlodel (bromocriptine mesylate). Although Parlodel therapy will effectively lower plasma levels of prolactin in patients with stitutes there are a considerable and a selectively lower plasma levels of prolactin in patients with stitutes there are a considerable and a selectively lower plasma levels of prolactin in patients with pituitary tumors, this does not obviate the necessity of radiotherapy or surgical procedures where appropriate. If pregnancy occurs, treatment should be discontinued immediately.

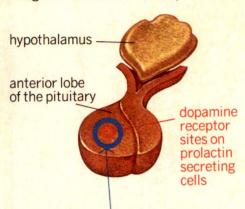
In postpartum studies, hypotension (decrease in supine systolic and diastolic pressures of greater than 20 mm and 10 mm Hg respectively) has been observed in almost 30% of patients; on occasion, supine systolic pressure dropped as much as 50 to 59 mm Hg. It is likely that many of these hypotensive episodes were not drug induced, since decreases in blood pressure are frequently noted during the puerperium independent of

drug therapy. Since Parlodel (bromocriptine mesylate) is known to cause hypotension in some patients, however, Parlodel therapy should not be initiated until the vital signs have been stabilized and no sooner than four hours after delivery. Periodic monitoring of the blood pressure, particularly during the first few days of therapy, is advisable and care should be exercised during concomitant administration with other medications known to lower blood pressure. Since dizziness (8% to 16%) and syncope (less than 1%) have been reported, patients should be cautioned about engaging in activities requiring rapid and precise responses, such as driving an automobile or operating dangerous machinery.

Precautions: Since treatment of amenorrhea/galactorrhea may result in restoration of fertility, patients should be required to use contraceptive measures, other than the oral contraceptives, during treatment; however, since patients often ignore this recommenda-

# The action of Parlodel bromocriptine mesylate compared with that of hormones in the prevention of postpartum lactation

With the shedding of the placenta following birth, estrogen and progesterone levels fall dramatically. Consequently, the lactogenic effects of elevated prolactin on the mammary gland are no longer blocked by these steroids.



### Parlodel site of action

Parlodel (bromocriptine mesylate), as a dopamine receptor agonist, reduces prolactin levels by acting directly on dopamine receptor sites on prolactin secreting cells in the anterior pituitary. With the rapid decline of prolactin levels, the stimulus leading to and supporting lactation is removed, and congestion and engorgement are prevented. Parlodel (bromocriptine mesylate) is not known to act directly on mammary tissue.



### Hormonal site of action

Estrogens, which actually stimulate prolactin secretion, are thought to inhibit the binding of prolactin to its receptors in the mammary glandular cells responsible for milk secretion. Estrogens prevent lactation by blocking the lactogenic effects of prolactin in a manner similar to the effects of estrogen during pregnancy. Since prolactin levels remain elevated, congestion and engorgement are possible.

the first nonestrogenic, nonhormonal agent for the prevention of postpartum lactation

# 2.5 mg bid with meals for 14 days (if necessary, may be continued for an additional 7 days)

bromocriptine mes



SANDOZ PHARMACEUTICALS, EAST HANOVER, NJ 07936

tion and since pregnancy may occur prior to reinitiation of menses, as an additional precaution, a pregnancy test is recommended at least every four weeks during the amenorrheic period and, once menses are reinitiated, every time a patient misses a menstrual period. Parlodel therapy has been demonstrated to be effective in the short-term management of amenorrhea/galactorrhea; data are not available on the safety or effectiveness of its use in long-term continuous dosage or in patients given repeated courses of treatment following recurrence of amenorrhea/galactorrhea after initial treatment. Recurrence rates are reportedly very high, ranging from 70% to 80% in domestic and foreign studies.

Decreases in blood pressure are common during the puerperium and, since Parlodel therapy produces hypotension in some patients, the drug should not be administered until the vital signs have been stabilized, and care should be exercised when it is administered concomitantly with other medications known to lower blood pressure. Safety and efficacy have not been established in patients with renal or hepatic disease. Diuretics and phenothiazines should be avoided during Parlodel therapy.

\*\*Nursing Mothers\*\*: Since it prevents lactation, the drug should not be administered to mothers who elect to breast feed their offspring.

\*\*Pediatric Use\*\*: Safety and efficacy have not been established in children under the age of 15.

\*\*Use in Pregnancy\*\*: Safe use has not been established.

Use in Pregnancy: Safe use has not been established.

Adverse Reactions: The incidence of adverse effects is quite high (68%) in patients Adverse Reactions: The incidence of adverse effects is quite flight (6%) in patients treated for amenorrhea/galactorrhea, but only 23% of patients treated within the recommended dosage range for prevention of physiological lactation had at least one side effect. Adverse reactions were generally mild to moderate and required discontinuation of therapy in only 6% of patients treated for amenorrhea/galactorrhea and 3% of patients treated for prevention of physiological lactation. A hypotensive effect, usually transient, may accompany treatment; two reports of fainting in the puerperium may possibly be related to this effect. The occurrence of adverse reactions may be lessened by temporarily reducing dosage to one-half tablet two to three times daily. The following table shows the most frequent adverse reactions

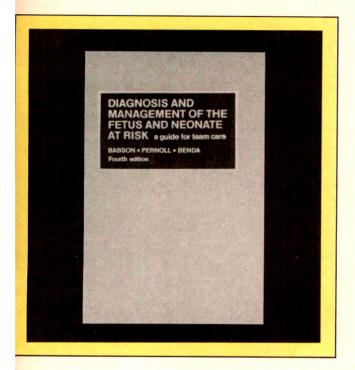
Treatment of Amenorrhea/ Galactorrhea	Adverse Reaction	Prevention of Lactation	
51%	Nausea	7%	
18%	Headache	10%	
16%	Dizziness	8%	
8%	Fatique	1%	
7%	Abdominal Cramps	0.4%	
6%	Lightheadedness		
5%	Vomiting	3%	
5%	Nasal Congestion	_	
3%	Constipation	_	
3%	Diarrhea	0.4%	
	Syncope	0.7%	
	Hypotension	28%	

Dosage and Administration: In amenorrhea/galactorrhea, the therapeutic dosage is one 2.5-mg tablet, two or three times daily with meals, and duration of treatment not to exceed six months; it is recommended that treatment commence with one tablet daily, increasing to a therapeutic dosage within the first week, to reduce the possibility of adverse reactions. In prevention of physiological lactation, therapy should be started only after the patient's vital signs have been stabilized and no sooner than four hours. after delivery; the recommended therapeutic dosage is one 2.5-mg tablet twice daily with meals; the usual dosage range is from one 2.5-mg tablet daily to one 2.5-mg tablet three times daily with meals; therapy should be continued for 14 days, however, may be given for up to 21 days if necessary. **How Supplied:** Tablets, 2½ mg, in packages of 30.

Before prescribing or administering, see package circular for full product information.

### When your depend potients depend on you...

## DEPEND

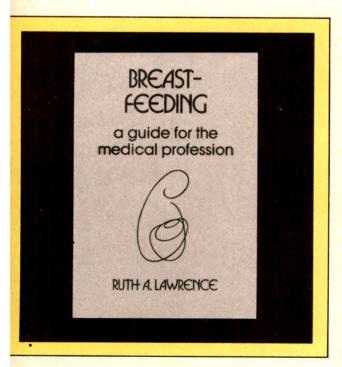


New 4th Edition!

DIAGNOSIS AND MANAGEMENT OF THE FETUS AND NEONATE AT RISK: A Guide for Team Care By S. Gorham Babson, M.D.; Martin L. Pernoll, M.D.; Gerda I. Benda, M.D.; with the assistance of Katherine Simpson, R.N.

Through three successful editions, you and your colleagues have depended on this reference for a comprehensive, down-to-earth view of perinatal care. This edition continues — and exceeds — that tradition of excellence. Stressing the team approach, it details the information you need to identify and manage the high risk mother, fetus and infant. Carefully updated sections:

- discuss diagnosis and management of the high risk neonate and fetus
- explain serious obstetrical problems and the perinate
- explore specific neonatal problems
- outline perinatal outcomes
- review the prevention of high risk pregnancy October, 1979. 358 pages, 99 illustrations. Price, \$21.95.



A New Book!

BREAST-FEEDING: A Guide for the Medical Profession By Ruth A. Lawrence, M.D.

Written by a highly respected authority in pediatrics, this reference focuses on the timely topic of breast-feeding. It also studies the advantages and disadvantages of breast-feeding.

Part I focuses on clinical aspects. You'll benefit from up-to-minute data on lactation and human milk — including pertinent anatomy, physiology, biochemistry and synthesis of human milk.

Part II offers a practical review of the overall medical management of the mother-infant team. The effects of drugs on breast milk, inducing lactation and nutritional aspects of human milk are just a few of the topics you'll explore. You'll be particularly interested in noteworthy discussions on:

- parent-infant bonding examines the motherinfant interaction in terms of psychology and personality differences between breast- and bottle-fed babies and mothers
- drugs in breast milk considers factors which influence drug passage into milk and possible effects on the nursing infant

October, 1979. 384 pages, 110 illustrations. Price, \$14.95.

# UN MOSBY!

A New Book!

EMERGENCY TRANSFER OF THE HIGH-RISK NEONATE: A Working Manual for Medical, Nursing and Administrative Personnel

By Angelo Ferrara, M.D., Ph.D. and Anantham Harin, M.D.

Whether you're organizing a neonatal/maternal transport system, actively involved in one now, or evaluating the performance of your present system — this new book will give you valuable information you will use. Based on the country's largest, most sophisticated and efficient transport system (the New York Infant Transport Service), this volume shows you how to adapt specific methods and procedures to your needs. The book's three sections illustrate its scope and organization:

PART I — "Organization and Administrative Concepts"

PART II — "Clinical Experience"

PART III — "Concepts of Evaluation"
December, 1979. 366 pages, 82 illustrations. Price, \$22.50.

A New Book!

OBSTETRICAL PRACTICE

Edited by Silvio Aladjem, M.D.; with 50 contributors.

Using a multidisciplinary approach, Dr. Aladjem and a team of distinguished contributors combine their expertise to provide a clear perspective and innovative approach to the problems encountered in day-to-day obstetrical practice. Logically organized in two parts — normal and abnormal obstetrics — this easy-to-read volume contains authoritative, up-to-date information on key areas in obstetrics. Among the topics examined in this well-illustrated text, you'll find:

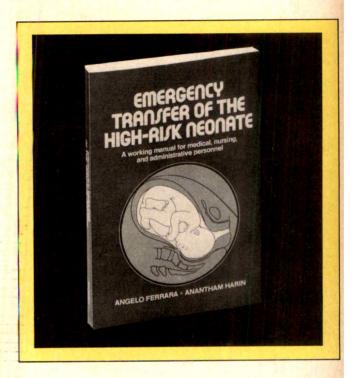
psychosomatic aspects of obstetrics — the factors determining a woman's coping mechanisms and the obstetrician's role in resolving problems during pregnancy and after

maternal-paternal-infant bonding relationship —
methods professionals can use to help the family
deal with perinatal stresses and establish close
attachments

 infections in obstetrics — viral, protozoal, fungal, and bacterial infections that challenge the physician responsible for the health care of the pregnant woman and fetus

management of cancer duing pregnancy — the management of the pregnant patient with gynecologic or nongynecologic cancer

September, 1980. Approx. 992 pages, 415 illustrations. About \$29.95.



### ALSO OF INTEREST

New 2nd Edition!

CLINICAL PERINATOLOGY

Edited by Silvio Aladjem, M.D.; Audrey K. Brown, M.D.; and Claude Sureau, M.D.; with 45 contributors.

December, 1979. 638 pages, 286 illustrations and two full-color plates. Price, \$49.50.

To order your 30-day on-approval copies, CALL US! Dial toll-free (800) 325-4177, ext. 10. In Missouri, call collect (314) 872-8370, ext. 10 during our regular business hours. MasterCard, VISA, or C.O.D. accepted.

All prices subject to change. Add sales tax if applicable.

AMS180



THE C. V. MOSBY COMPANY 11830 WESTLINE INDUSTRIAL DRIVE ST. LOUIS, MISSOURI 63141

### Medical Genetics Fellowship at NIH

An NIH Associate Training Program.

The Interinstitute Medical Genetics Fellowship Program of the National Institutes of Health offers fellowships providing a comprehensive clinical and laboratory experience in medical genetics. The fellowships begin July 1, 1981 and 1982 and are offered for two years. There is a possibility of extension of the appointment for a third year. Applications are invited from individuals of the highest caliber with the M.D. or M.D.-Ph.D. degree who are seriously interested in pursuing careers in academic medicine and research. Clinical training involves inpatient and outpatient services at the NIH 480 bed research and teaching hospital, which with collaborating medical facilities provides a broad exposure to biochemical and

cytogenetics, prenatal diagnosis, genetic counseling, screening techniques, and population genetics. Exceptional research opportunities exist in the Institutes' multiple laboratories. The program staff includes scientists and physicians of international stature.

Candidates who qualify for appointment in the Public Health Service Commissioned Corps receive a starting salary of \$22,332, a portion of which is tax exempt. An additional salary increase may be possible in the third year. Moving and travel expenses are paid and health care is free. Comparable civilain fellowships are also available. Interested candidates should submit their curriculum vitae to or request further information from:

The Associate Program
Building 31, Room 4B04
National Institutes of Health
Bethesda, MD 20205
Public Health Service
Telephone — 301-496-2427



An Equal Opportunity Employer

### OB/GYN

BOARD CERTIFIED OR ELIGIBLE to join large multispecialty group in San Francisco. Large volume high-risk obstetrical service; over 3000 deliveries/year; 12 staff ob/gyn; 4 year residency program in ob/gyn. Fringes include excellent vacation and educational leave, malpractice and life insurance, disability, retirement benefits. Academic appointment available.

Send inquiry and C.V. to:

Ira Golditch, M.D.
Chief, Dept. Ob/Gyn
Kaiser/Permanente Medical Center
2200 O'Farrell Street
San Francisco, CA 94115
or call (415) 929-4845

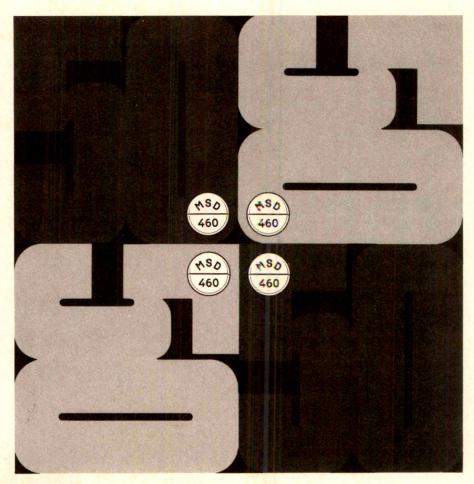
### MATERNAL/ FETAL MEDICINE

OB/GYN PERINATOLOGIST with certification or board eligibility in Maternal-Fetal Medicine for large perinatal center in San Francisco; large volume high-risk obstetric service, over 3000 deliveries/year; 4 year residency program in ob/gyn; 17 staff obstetricians in large multispecialty group; excellent opportunity for clinical practice and research; academic appointment available. Anticipate starting in or prior to 7/81.

Send inquiry and C.V. to:

Ira Golditch, M.D.
Chief, Dept. Ob/Gyn
Kaiser Permanente Medical Center
2200 O'Farrell Street
San Francisco, CA 94115
or call (415) 929-4845

for neurogenic atony of the urinary bladder with retention, higher titrated dosages may be needed (up to 200 mg/day)



# **MSD** announces

(BETHANECHOL CHLORIDE | MSD)

when higher titrated dosages are indicated

After titration, dosages as high as 50 mg t.i.d. or q.i.d. have been effectively employed in neurogenic atony of the urinary bladder as well as for the treatment of postoperative and postpartum nonobstructive (functional) urinary retention.

- Helps to initiate micturition and empty the bladder.
- Helps to reduce the frequency of bladder catheterization. Contraindicated in hypersensitivity to

URECHOLINE, hyperthyroidism, pregnancy, peptic ulcer, latent or active bronchial asthma, pronounced bradycardia or hypotension, vasomotor instability, coronary artery disease, epilepsy, and parkinsonism.

URECHOLINE should not be used when the strength or integrity of the gastrointestinal or bladder wall is in question or in the presence of mechanical obstruction. If necessary, the effects of the drug can be abolished promptly by atropine.

for neurogenic atony of the urinary bladder with retention, higher titrated dosages may be needed (up to 200 mg/day)

# 50-mg TABLETS URECHOLINE® (BETHANECHOL CHLORIDE | MSD)



Contraindications: Hypersensitivity to Tablets URECHOLINE (Bethanechol Chloride, MSD) or to any component of Injection URECHOLINE; hyperthyroidism, pregnancy, peptic ulcer, latent or active bronchial asthma, pronounced bradycardia or hypotension, vasomotor instability, coronary artery disease, epilepsy, and parkinsonism. Should not be employed when the strength or integrity of the gastrointestinal or bladder wall is in question, or in the presence of mechanical obstruction; when increased muscular activity of the gastrointestinal tract or urinary bladder might prove harmful, as following recent urinary bladder surgery, gastrointestinal resection and anastomosis, or when there is possible gastrointestinal obstruction; in bladder neck obstruction, spastic gastrointestinal disturbances, acute inflammatory lesions of the gastrointestinal tract, or peritonitis; or in marked vagotonia.

Warnings: The sterile solution is for subcutaneous use only. It should never be given intramuscularly or intravenously. Violent symptoms of cholinergic overstimulation, such as circulatory collapse, fall in blood pressure, abdominal cramps, bloody diarrhea, shock, or sudden cardiac arrest are likely to occur if the drug is given by either of these routes. Although rare, these same symptoms have occurred after subcutaneous injection, and may occur in cases of hypersensitivity or overdosage.

**Precautions:** Special care is required in patients receiving ganglion blocking compounds because a critical fall in blood pressure may occur; usually, severe abdominal symptoms appear before there is such a fall in blood pressure. In urinary retention, if the sphincter fails to relax as the drug contracts the

bladder, urine may be forced up the ureter into the kidney pelvis; if there is bacteriuria, this may cause reflux infection.

Adverse Reactions: Abdominal discomfort, salivation, flushing of the skin ("hot feeling"), sweating. Large doses more commonly result in effects of parasympathetic stimulation, such as malaise, headache, sensation of heat about the face, flushing, colicky pain, diarrhea, nausea and belching, abdominal cramps, borborygmi, asthmatic attacks, and fall in blood pressure.

Atropine is a specific antidote. The recommended dose for adults is 0.6 mg (1/100 grain). The recommended dosage in infants and children up to 12 years of age is 0.01 mg/kg repeated every two hours as needed until the desired effect is obtained, or adverse effects of atropine preclude further usage. The maximum single dose should not exceed 0.4 mg. Subcutaneous injection of atropine is preferred except in emergencies when the intravenous route may be employed. When Injection URECHOLINE is used, a syringe of atropine sulfate should always be available.

**How Supplied:** Tablets, containing 5 mg, 10 mg, 25 mg, or 50 mg bethanechol chloride each, in bottles of 100 and single-unit packages of 100; Injection, 5 mg per ml, is a clear, colorless solution, and is supplied in boxes of 6 × 1-ml vials.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, PA 19486

MERCK SHARP. DOHME

J9URO2(426)

## FETUS, PLACENTA, AND NEWBORN

### Biophysics of the developing heart

### I. The force-interval relationship

PAGE A. W. ANDERSON\*
ANDRÉS MANRING
CARLYLE CRENSHAW, JR.
Durham, North Carolina

The force-interval relationship was evaluated in the developing heart of the lamb. The qualitative characteristics of the relationship were the same in isolated muscle (from 93 to 141 days' gestation to 1 year old) as in the chronically instrumented in utero fetus (122 to 141 days' gestation): (1) contractility, e.g., the maximum rate of rise of force, increased monotonically from a small value immediately after a contraction to a plateau, and (2) postextrasystolic potentiation was present in all preparations. In the intact animal, postextrasystolic potentiation depended on the basic pacing interval, t<sub>0</sub>, and the timing of the extrasystole, t<sub>1</sub>: when t<sub>0</sub> was held constant and t<sub>1</sub> was increased, potentiation decreased; when t<sub>1</sub> was held constant and t<sub>0</sub> was increased, potentiation increased. The qualitative characteristics of the relationship, and so the under ring myocardial basis, were unchanged over the developmental period studied. (AM. J. OBSTET. GYNECOL. 138:33, 1980.)

Some studies suggest that contractility may not change with development, é.g., force per cross-sectional area (obtained by morphometric techniques¹) or the ability of glycerinated muscle to generate tension² is not different at several developmental stages. This is surprising in view of the significant developmental changes in other characteristics of the heart, e.g., morphologic

From the Duke University Medical Center.

This work was supported in part by National Institutes of Health Grants HL-20749, HL-11307, and HL-18270, and by the National Foundation—March of Dimes.

Received for publication December 26, 1979.

Revised March 7, 1980.

Accepted March 13, 1980.

Reprint requests: Page A. W. Anderson, M.D., Box 3218, Duke University Medical Center, Durham, North Carolina 27710.

\*Recipient of Research Career Development Award Grant No. HL-00500.

changes.3, 4 A more sensitive indicator might reveal devebpmental changes in contractility and might also provide insights into the mechanisms that underlie cardiac contractility. The force-interval relationship of cardiac muscle (which describes the effect of the interval between stimuli on the development of force or presure) is a candidate for such an indicator of contractility: in the adult heart it provides a sensitive indicator of changes in inotropy5, 6 as well as a prognostic test for the onset of hypertrophy and the development of Feart failure.7, 8 The force-interval relationship has also been described as undergoing developmental changes: the amount of potentiation produced by paired pacing is less in the hearts of the fetal lamb and newborn kitten than in the adult heart of the sheep and cat. 5. 10 These results point out the potential value of • the Force-interval relationship in evaluating changes in contractility that take place with development and birth.

Tais study describes the general characteristics of the . ..

force-interval relationship during the last third of gestation and after birth in the sheep. These qualitative characteristics of the relationship are described in the developing myocardium, both in vitro and in vivo, for the first time. Two kinds of cardiac preparations were used: (1) Isolated muscle was held isometric to study the pure effects of the interval between beats on the force of contraction and to compare the responses of hearts from the last third of gestation and the neonatal period to those of the adult heart. (2) The heart of the fetal lamb was chronically instrumented to allow the investigation of this relationship in the intact developing animal. The results in the intact fetal animal describe how postextrasystolic potentiation depends on heart rate and the timing of the extrasystole, and how left ventricular end-diastolic dimension and aortic diastolic pressure can modify these results.

Subsequent articles in this series will describe (1) the effects of changing muscle length and/or ventricular volume and the effects of altering the inotropic state on the force-interval relationship, (2) the cardiovascular changes that occur with birth, and (3) quantitative changes in the force-interval relationship that occur with fetal development and after birth, comparing the developmental time course observed in the isolated myocardium to that of the intact heart and comparing the changes in this relationship to other concomitant cardiovascular changes in the intact animal.

### Methods

. Isolated muscle preparation. A trabeculae carneae cordis (N = 10) or moderator muscle (N = 11) was isolated from the heart of a fetal (N = 13) or postpartum (N = 8) lamb. The fetal lambs were from agedated pregnancies (gestation, 93 to 141 days) of mixed-breed ewes. The postpartum sheep ranged in age from 1 day of age to adulthood.

The ewes were anesthetized with intravenous ketamine (15 to 30 mg/kg). The uterus was exposed by a midline abdominal incision, and a hysterotomy was performed over the fourth left intercostal space. A thoracotomy was performed and the heart excised within 30 seconds and placed in warmed Krebs-Henseleit solution<sup>11</sup> aerated with 95% O<sub>2</sub> and 5% CO<sub>2</sub>. The postpartum lambs were anesthetized with intravenous ketamine, a thoracotomy was performed, and the heart was rapidly excised and placed in warmed Krebs-Henseleit solution.

The thinnest muscle (cross-sectional area, 0.18 to 4.15 sq mm,  $1.9 \pm 0.3 \text{ sq mm}$ , SE) from the right cr left ventricle was selected for study. The muscles were mounted isometrically in a temperature-controlled bath at the ovine body temperature, 39° C. The muscle was superfused with Krebs-Henseleit solution at 5 ml/min. The bath, mounting of the tissue, and method of stimulation have been described previously.7

The force signal (Statham force transducer, UC-2) was filtered (Tektronics AM 402, frequency response 0 to 300 hertz), digitized at 1 kilohertz, and analyzed by a computer (PDP 11). The computer printout listed: the peak force  $(\overline{F})$ , peak rate of rise of force  $(\dot{F}_{max})$ , the timing of the test stimuli relative to the last regularly paced regular stimulus, and the times following the respective stimulus required for the contraction to reach  $F_{max}$  and  $\overline{F}$ . Fused contractions (degree of fusion, greater than 20%) were eliminated from the data.

### Intact animal preparation.

Surgical preparation. Instrumentation of the cardiovascular system was carried out in seven fetal lambs from age-dated singleton pregnancies (gestation, 119 to 132 days) of mixed-breed ewes. Twenty-four to 72 hours preoperatively, the ewe was placed in a pen in the room that connected through the physiology laboratory to the operating room. The ewe was fasted for 24 hours prior to operation.

An external jugular intravenous infusion of ketamine (1 to 4 mg/L) was begun preoperatively and was continued throughout the surgical procedure. Oxygen was administered by a nasopharyngeal catheter at 8 L/min. The abdomen was shaved, scrubbed sequentially with pHisoHex and Betadine, and draped. A low midline abdominal incision was made and the uterus was exposed. The portion of the uterus containing the fetal head was delivered through the abdominal incision. A hysterotomy was made parallel to the fetal trachea and extended through the fetal skin. The skin was marsupialized to the uterine wall with Babcock clamps in order to minimize loss of amniotic fluid. A No. 5 NIH angiographic catheter was introduced into the superior vena cava via the jugular vein, and another angiographic catheter was introduced into the brachiocephalic trunk via the common carotid artery. After the catheters were sutured into place, an electrocardiographic lead was sutured to the subcutaneous tissue. The fetal skin and uterine wall were closed in layers, with 10 cm of the catheters and leads left within the amniotic space, and, if possible, that portion of the uterus was returned to the abdomen. The portion of the uterus containing the thorax was delivered, and a hysterotomy was made over the fourth left anterior lateral intercostal space. The fetal skin was incised and marsupialized to the uterine wall. A thoracotomy was performed and the pericardium was opened, and the apex of the heart was delivered through the thoracotomy. Left ventricular minor axis distance transducers, 3.0 mm in diameter piezoelectric crystals, 5 mHz, Transducer Products, were inserted through ventricular puncture wounds into the ventricular cavity and pulled back to the endocardial surface. Care was taken to place the transducers in a configuration that most closely represented the minor axis dimension. A micromanometer pressure transducer (Narco Biosystems), 3.5 mm in diameter, resonant frequency 15 kHz, frequency response 1.5 kHz, was introduced into the left ventricle through an apical stab wound and fixed in place with a mattress suture. A left atrial catheter, Tygon tubing HL-54, inside diameter 0.03 inch, outside diameter 0.048 inch, was introduced through the left atrial appendage and fixed in place with a mattress suture. Atrial pacing electrodes were glued to the left atrial appendage and held in place by suturing to the pericardium. A pleural catheter (Tygon HL-50) was placed at the level of the left ventricle, and the ribs were approximated. A subcutaneous electrocardiographic lead was sutured in place and the skin was, closed. An amniotic catheter (Tygon tubing HL-50) was sutured to the skin at the level of the heart on the left side of the thorax. The leads and catheters were brought through the hysterotomy, with 10 cm left in the amniotic space. Ampicillin, 0.1 gm, was administered intravenously to the fetus, and 0.9 gm was instilled in the amniotic space, and the uterus was closed. The catheters and leads were brought through the midline abdominal incision. After the peritoneum was closed, the catheters and leads were passed through a subcutaneous tunnel to the left side of the ewe and through a 1-cm incision in the skin. The abdominal incision was closed. A Dacron pocket with a Velcrolined opening was sutured to the skin to cover the catheters and leads. The intravenous infusion was discontinued, and the ewe was returned to her pen. The ewe was usually standing and eating within 10 to 15 minutes after completion of the procedure.

Preparation stability. Beginning on the first day after instrumentation, the ewe was familiarized with the laboratory by putting her in a rolling cage and taking her into the laboratory. The cage and equipment were arranged to let the ewe see the sheep in the adjoining room. Hay and alfalfa pellets were provided for her. This arrangement and conditioning resulted in the ewe's being quiet and apparently calm during the studies. This was important since excitement of the ewe was often associated with an increase in the fetal heart rate, left ventricular pressure, and/or peak derivative of left ventricular pressure (Pmax).

Each day the fetus was monitored by attaching the instrumentation leads to the physiologic recording system. The pacing protocol was not initiated until at least 3 days after the operation. The fetal arterial Po<sub>2</sub>

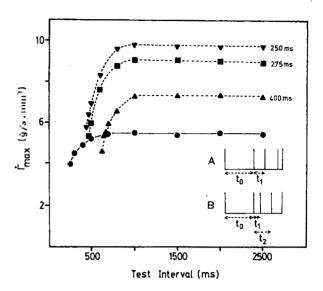


Fig. 1. The force-interval curves, Fmax (the maximum rate of rise of force) described as a function of the test interval (t<sub>1</sub> or 💈 from an isolated fetal trabeculae carneae cordis, 132 days' gestation, are illustrated: the basic interval,  $t_0 = 3,000$  msec, the first-stage curve with varying t<sub>1</sub> (circles), and three second-stage curves with fixed first test intervals and varying  $t_2 = 250$  msec (inverted triangles),  $t_1 = 275$  msec (squares), and  $t_1 = 400$  msec (upright triangles). The inset is a schematic representation of the pacing sequence of the two-stage experiment. A describes the first stage, and B, the second stage.

ranged between 20 and 29 mm Hg, the Pco2 between 38 and 44 mm Hg, and the pH between 7.345 and 7.39. Similar values were obtained from chronically instrumented fetal lambs that underwent less extensive surgical procedures. 12, 13 On the first postoperative day ezch lamb had a tachycardia with rates ranging from 170 to 200/min. Although the range was large, the rate was almost constant in each lamb, varying less than 5% on the first postoperative day. By the third day the range of heart rates had fallen to 150 to 175/min in five lambs, and by the fifth day in all the lambs. These rates semetimes showed slow or sudden periodic variations associated with maternal movement or excitement. Three to 4 days prior to birth the heart rate was 130 to 160/min. In the 24 hours prior to birth the rate would occasionally decrease to 100 to 120/min. This decrease was not always associated with an increase in intraamniotic pressure. Although the time course of change in heart rate postoperatively was more rapid in our lambs, the return of heart rate postoperatively and the results prior to birth were similar to those described by others.14 The lambs had about the same arterial blood gas, aortic pressure, or peak rate of rise of left ventricular pressure (when paced at the same heart rate) regardless of the time course of heart rate changes after operation.

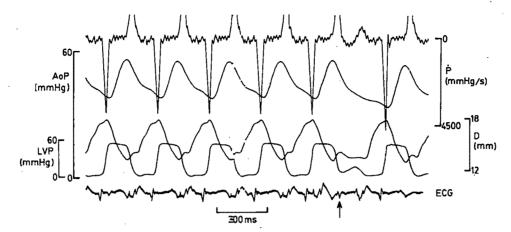


Fig. 2. The results from a chronically instrumented in utero fetal lamb, 134 days' gestation, 15 days after instrumentation, are illustrated: the basic cycle interval,  $t_0 = 300$  msec, and the first test interval,  $t_1 = 195$  msec. The arrow denotes the QES of the first test systole. The traces from top to bottom are:  $\dot{P}$ , the first derivative of left ventricular pressure; AoP, aortic pressure; D, left ventricular minor axis dimension; LVP, left ventricular pressure; ECG, electrocardiogram.

At the resting unpaced rate,  $\dot{P}_{max}$  ranged from 1,400 mm Hg/sec to 2,400 mm Hg/sec, with a mean similar to the value of 2,300 mm Hg/sec described by others. The peak systolic arterial pressure of 40 to 65 mm Hg was similar to that of other chronically instrumented fetal lambs, 4 as was the gradual increase in peak systolic pressure with age. The left ventricular encidiastolic pressure also was in the physiologic range of 2 to 8 mm Hg.15

Six of the seven lambs were born alive and in good health, thus providing further reassurance of the good state of health of the lambs in utero. The seventh died during an unassisted birth; the catheters and leads allowed only the head and forelegs to be delivered.

We imposed two criteria for stability of the fetus during the experiments: (1) The intrinsic heart rate was measured before and after every two-stage experiment (see below), and the lamb was judged to be in a stable state if these rates differed by less than 5%. (2) If, for systoles with the same left ventricular end-diastolic dimension (EDD),  $P_{max}$  at a given paced rate changed by less than 5% during the two-stage experiment, the lamb was judged to be in a stable state. Unless both criteria were met, the data were not used to generate  $P_{max}$ -interval curves (see Figs. 3 and 4) and  $P_{max}$ -interval ratios (see Figs. 5 and 6).

Acquisition and recording of data. During the pacing protocol, the left ventricular pressure, arterial pressure, P<sub>max</sub>, left ventricular dimensions, and the electrocardiogram were continuously monitored. The pressure waveforms from the fluid-filled systems were obtained with Statham pressure transducers, P231D, and Hewlett-Packard carrier preamplifiers 350-1100C. The amniotic pressure was subtracted from fetal pressures.

The system was statically calibrated with a mercury manometer. The sonomicrometry system, used to measure left ventricular dimensions, had a minimum resolution of 0.07 mm and was linear under the conditions of these studies.14 Electronic drift was less than 0.05 mm per hour; the signals were calibrated by substituting electronic time delays in the circuit. The left ventricular pressure waveform was calibrated with the use of the arterial and the left atrial or superior vena caval pressure.14 The ventricular waveform was differentiated with an analogue differentiator (0 to 100 Hz frequency response). The electrocardiogram was obtained with a Bioamplifier 2122 (Bio Com, Inc). The interval between systoles was measured continuously by means of a digital counter that was triggered by the QRS complex of the electrocardiogram. These intervals allowed us to determine whether the heart rate was being controlled by the atrial pacing, and provided the precise time that the ventricular depolarization of the test systoles followed the previous regular QRS. Waveforms were recorded on an Ampex 1300 FM tape recorder (7.5 inches per second) to be reproduced later on a Grass oscillographic recorder (5 inches per second) or an Elema Mingograph 800 paper recorder (250 mm/sec). Portions of the studies were simultaneously recorded with the Grass recorder (5 in/sec).

### Force-interval experiment.

Isolated muscle. The muscle was paced at a constant rate of 0.33 Hz. Two test stimuli were interpolated, periodically and infrequently, between every eighth and ninth stimulus at the basic rate or pacing interval,  $t_0$ . The intervals between the first and second test stimulus and the previous regular stimulus,  $t_1$  and  $t_2$ , were varied systematically in two stages. The various

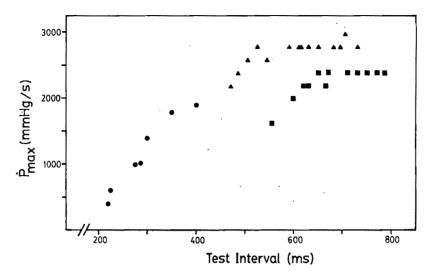


Fig. 3. The P<sub>max</sub>-interval curves, [P<sub>max</sub> (the maximum rate of rise of interventricular pressure) described as a function of the test interval (t<sub>1</sub> or t<sub>2</sub>)], for a chronically instrumented in utero lamb, 139 days' gestation, 17 days postoperatively. The first-stage results (circles) and the results from two second-stage experiments (triangles and squares) are illustrated for a basic interval, to = 400 msec. The fixed first test intervals for the two second-stage experiments were  $t_1 = 225$  ms (triangles) and  $t_1 = 285 \text{ msec (squares)}.$ 

intervals  $t_0$  (=1/rate),  $t_1$ , and  $t_2$  are depicted schematically in Fig. 1 (A and B).

During the first-stage experiment, t2 was held fixed at 2,700 milliseconds, and t<sub>1</sub> was varied between 275 msec and 2,500 msec (circles, Fig. 1). During the second-stage experiment, t<sub>1</sub> was held fixed, e.g., 300, 400, and 500 msec; for each fixed value of t1, t2 was varied between  $t_1 + 300$  msec and 2,500 msec.  $F_{max}$  of the second test contraction was plotted against t2 (squares and triangles in Fig. 1).

The plateau value of the second-stage curve (see Fig. 1, e.g.,  $\dot{F}_{max}$  at  $t_2 = 2,500$  msec) divided by the plateau value of the first-stage curve (see Fig. 1, e.g., Fmax at  $t_1 = 2,500$  msec) was called the  $\dot{F}_{max}$ -interval ratio. The F<sub>max</sub>-interval ratio was sampled several times throughout the experiment in order to test the stability of the contractile response. An increase or decrease of greater than 10% of this ratio during an experiment was considered to be significant and resulted in the elimination of the data.

The above-mentioned pacing protocol for the isolated muscle experiments was modified for use in the intact animal because the intrinsic heart rate and the properties of the atrioventricular conduction system did not allow the same pacing patterns to be used. The heart rate was controlled by atrial pacing. A digital programmable stimulator provided the pulse sequence. This generator triggered an isolated stimulator (Devices isolated stimulator DS2) that triggered a second isolated unit (ISB 2.5, Stoelting Co.). The stimulating pulses were 5 to 15 msec in duration and 10% above threshold voltage.

During each experiment, the basic paced heart rate (=1/t<sub>0</sub>) was constant. Trains of 15 stimuli were delivered to the heart. The trains were separated by a pause equal to 3 to. During this pause, two test stimuli were delivered to the atrium at variable times. The intervals at which the two test ventricular depolarizations followed that of the last regular systole in the train were termed t<sub>1</sub> and t<sub>2</sub>, respectively (see Figs. 2 and 3). The test intervals t1 and t2 were varied systematically, similar to the description in the previous section. The specific values of t1 and t2 were different from the values noted in the isolated muscle section, e.g., in the intact fetal animal,  $t_0 = 350$  msec,  $t_1 = 210$  msec, and  $t_2 = 550$ msec, as compared to  $t_0 = 3,000$  msec,  $t_1 = 300$  msec, and  $t_2 = 2,500$  msec for the isolated muscle experiments. Whenever possible, the force-interval relationship was evaluated with the use of standard basic intervals ( $t_0 = 300$ , or 400 msec) and test intervals (e.g., a range of  $t_1 = 180$  to 260 msec). In general, the greater the gestational age of the lamb, the longer the refractory period of the atrioventricular conduction system became. In addition, usually the longer the basic pacing interval, to, the longer was the refractory period of the atrioventricular conduction system. At times, these changes in the refractory period of the atrioventricular conduction system prevented the shortest intervals of t<sub>1</sub> and t2 from being used in all the animals throughout the gestational ages studied. Similarly, the longest basic interval,  $t_0 = 400$  msec, could not be used throughout gestation because the intrinsic heart rate was too fast until approximately 7 days prior to birth.

Like the results of the isolated muscle experiments, P<sub>max</sub> of the test systoles in the first stage of the experiment was plotted as a function of t1. In the second-stage experiment, Pmax for the test systoles following the first test systole (premature systole) with a fixed t1 was plotted as a function of t2. The Pmax-interval ratio (Pmax of the postextrasystolic potentiated test beat divided by P<sub>max</sub> of the preceding regular beat), formed from systoles preceded by the same left ventricular enddiastolic dimension (EDD), was used to test for stability during the experiment, as the F<sub>max</sub>-interval ratio was used in the isolated muscle experiments.

### Results

Isolated muscle preparation. The ability of a muscle to generate force (peak force or Fmax) in response to a stimulus increased with time after a contraction. This increase was seen in the force-interval curves illustrated in Fig. 1. These were typical of the results obtained from all fetal and postnatal preparations regardless of age, from 93 days' gestation to adulthood. This increase in the values of  $\dot{F}_{max}$  for the first-stage values was described by a curve that rose monotonically with increasing  $t_1$  to a plateau value equal to  $\dot{F}_{max}$  of the previous regular contraction.

The ability to generate force after the first test contraction was similar to that after the regular contraction, in that the shorter the interval between the second test contraction and the preceding contraction, the smaller the value of peak force or  $\hat{F}_{max}$  generated. The curves of Fmax versus t2 (Fig. 1) that resulted from applying test contractions at different values of t2 (a different curve followed each first test contraction with a different fixed value of t<sub>1</sub>) were similar to those of the first stage-rising from the smallest value to larger values with an increase in t2 until a plateau value was reached. However, the second-stage curves rose more rapidly than the first-stage curve and to plateaus that were higher than the plateau of the first-stage curve. Postextrasystolic potentiation, illustrated by these higher plateaus, was found in all preparations studied A measure of this postextrasystolic potentiation is the F<sub>max</sub>-interval ratio, F<sub>max</sub> of the second-stage curve plateau divided by  $\dot{F}_{max}$  of the first-stage curve plateau (see "Methods"). In all preparations, the smaller that t1 was made, the higher the second-stage plateau became, and, consequently, the larger was the Fmax-interval ratio. The effect of increasing the pacing rate on the muscle's response to a given value of t1 and t2 was not examined systematically because fast pacing caused

rapid (and usually irreversible) deterioration in contractility.

Intact animal preparation. Each fetus was studied at least every other day, beginning 3 days after operation. The general characteristics of the results remained unchanged throughout the period of gestation studied, from 122 days' gestation to birth.

Fig. 2 shows the results obtained from a fetal lamb at 134 days' gestation and 15 days after instrumentation. Note the stability of the left ventricular end-diastolic (EDD) and end-systolic dimension, the peak systolic and diastolic aortic pressure, the left ventricular peak systolic and end-diastolic pressure, and Pmax prior to the introduction of the pause for the test systoles. The rise in ventricular pressure with the first test systole (denoted by the arrow) prevented the rapid filling phase after the previous regular systole. The diastolic fall in aortic pressure after the regular systole was uninterrupted by the first test systole because its peak systolic pressure was not sufficient to open the aortic valve. Although the peak ventricular pressure did not reach aortic pressure, the minor axis dimension decreased. This was accompanied by a prominent V wave in the left atrial pressure (not illustrated in the figure), suggestive of mitral regurgitation. Then, as ventricular pressure fell, ventricular filling began earlier and more rapidly than for the previous regular systoles. In this illustration, t2 was adjusted to make EDD for the second test systole equal to the EDD of the previous regular systole.  $\dot{P}_{max}$  of the second test systole was 20% greater than P<sub>max</sub> of the previous regular systole, thus demonstrating postextrasystolic potentiation, and markedly greater than P<sub>max</sub> of the first test systole. This value of Pmax of the test systole was reached before left ventricular ejection (which was marked by an abrupt shortening in the minor axis dimension).

Ventricular ejection during the second test systole was also altered by the previous test systole. The rate and the amount of shortening of the minor axis dimension were greater than in either the previous test systole or the regular systole. The enhancement of these characteristics might have been due to postextrasystolic potentiation, but might also have been due, in part, to the drop in aortic diastolic pressure (i.e., the afterload of the left ventricle), for diastolic pressure was lower at the beginning of ejection for the second test systole than it was for the regular systole.

In the intact heart, the P<sub>max</sub>-interval curves (Figs. 3 and 4) which described the relationship between the test interval and the ability of the test systole to develop pressure were similar to the force-interval relationship in isolated muscle (Fig. 1): The shorter the interval, the smaller the peak pressure or  $P_{max}$  (Figs. 3 and 4). When

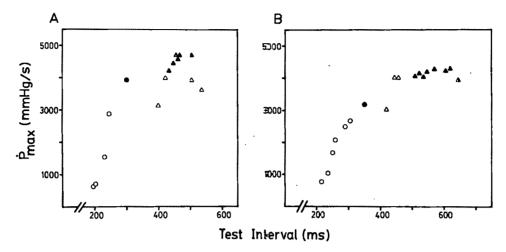


Fig. 4. A, The first-stage (circles) and second-stage (triangles) Pmax-interval curves for an in utero fetal lamb, 136 days' gestation, 14 days postoperatively, at a basic interval, to = 300 msec, and for the second-stage experiment,  $t_1 = 205$  msec. Solid symbols denote systoles of equal left ventricular end-diastolic dimension (EDD), and the open symbols are for test systoles with an EDD lesss than that of the previous regular systole (solid circle). B, The first-stage (circles) and second-stage (triangles) Pmax interval curves for the same fetal lamb in A studied on the same day at a slower basic cycle interval, to = 350 msec. The second-stage experiment had the same fixed first test interval, t1 = 205 msec, as in panel A. Solid symbols are for systoles with equal EDD; open symbols have a EDD less than that of the previous regular systole (solid circle), and the half-solid triangle is from a systole that has an EDD greater than that of the previous regular systole, but Pmax was obtained after left ventricular ejection had begun.

compared to Fig. 1, Fig. 3 illustrates the similarity of the P<sub>max</sub>-interval curves obtained from the intact heart to those from the isolated muscle. In this illustration, the first-stage (circles) and the two second-stage (triangles and squares) curves were obtained from a 139day-old fetus 17 days postoperatively. Each of the curves rose monotonically to a plateau with an increase in test interval. For the first stage, Pmax rose monotonically to  $\dot{P}_{max}$  of the previous regular systole (the circle at 400 msec) as t<sub>1</sub> was increased to t<sub>0</sub>. Both second-stage plateaus were higher than the first-stage plateau, thus illustrating postextrasystolic potentiation. The highest plateau (triangles), showing the greatest postextrasystolic potentiation, was obtained after the first test systole with the shorter t<sub>1</sub> (225 msec), whereas the intermediate plateau was obtained after the first test systole with the longer t<sub>1</sub> (285 msec).

Some of the points on the curves in Fig. 3 were not obtained at the same level of ventricualr filling, i.e., different values of EDD. For example, the EDD of the systoles of the rising phase were smaller than EDD during the plateau. Consequently, the shapes of these curves could not be compared with those obtained from isometric muscles, since the shapes of the P<sub>max</sub>interval curves illustrated in Fig. 3, as well as in Fig. 4, A and B, are the result of two different factors that affect  $P_{max}$ : the timing of the test systoles (1) altered  $P_{max}$ 

according to the force-interval relationship and (2) determined P<sub>max</sub> according to the Frank-Starling relationship by changing the amount of ventricular filling.

Fortunately, these effects can be more easily separated in the second-stage curves. In Fig. 4, A and B, the data obtained from the same fetus and on the same day (136 days' gestation, 14 days postoperatively) but at two different basic intervals (t<sub>0</sub> = 300, 350 msec) are illustrated. There was a brief period (50 to 75 msec), called the isolength range,6 during each second-stage curve when EDD of the test systoles was equal to EDD of the previous regular systole (solid symbols). In Fig. 4, A,  $t_0 = 300$  msec, during the isolength range,  $\dot{P}_{max}$  increased with an increase in t2 to reach a quasi-plateau in excess of  $P_{max}$  of the previous regular systole. This rise to a plateau is similar to a change in Fmax with an increase in t2 in the isolated muscle preparations (Fig. 1). In Fig. 4, B,  $t_0 = 350$  msec,  $\dot{P}_{max}$  remained at a quasiplateau in excess of P<sub>max</sub> of the previous regular systole as t2 was increased during the isolength range. The isolength portion of both of these curves demonstrated that postextrasystolic potentiation of Pmax is the result of the introduction of an extra systole and not merely . the consequence of a change in EDD. Similarly, the increase in contractility (Pmax) with an increase in ta over a portion of the isolength curve (Fig. 4, A) is a result of altering the pattern of stimulation and not the

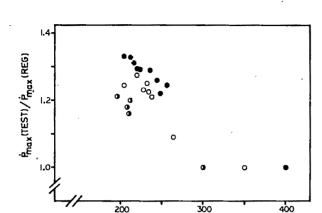


Fig. 5. The ratio of  $\dot{P}_{max}$  of the second test systole, postextrasystole, to  $\dot{P}_{max}$  of the previous regular systole ( $\dot{P}_{max}$ -interval ratio) for systoles with the same EDD is plotted as a function of the fixed first test interval,  $t_1$  for different basic intervals:  $t_0 = 400$  msec (solid circles),  $t_0 = 350$  msec (open circles), and  $t_0 = 300$  msec (half-solid circles): The fetus had a gestational age of 138 days, 14 days postoperatively.

TEST INTERVAL (ms)

result of an increase in EDD or Frank-Starling effect. These increases in  $\dot{P}_{max}$  with an increase in  $t_2$  during a portion of the isolength curve revealed a potential problem in describing postextrasystolic potentiation. If the  $\dot{P}_{max}$ -interval ratio, comparing the potentiated test systole to the previous regular systole, was obtained during the early portion of the isolength range in Fig. 4, A, small values of the ratio would have been obtained and postextrasystolic potentiation would have been underestimated. Thus, this ratio must be obtained only during the plateau portion of the isolength range.

The importance of monitoring EDD to interpret  $\dot{P}_{max}$ -interval curves or  $\dot{P}_{max}$ -interval ratios is demonstrated in Fig. 4, A. At the two longest values of  $t_2$ ,  $\dot{P}_{max}$  was less than  $\dot{P}_{max}$  of the previous regular systole. This did not result from a fall in contractility (i.e., postextrasystolic depression; cf. Reference 8), for EDD for these test systoles was smaller than EDD for the previous regular systole. Such variability in EDD occurred spontaneously, from beat to beat and from minute to minute, even when the heart rate was kept constant by pacing. If EDD had not been monitored, the results in Fig. 4, A, could have been mistaken for an absence of postextrasystolic potentiation.

Fig. 4, B shows another cause of this droop in  $\dot{P}_{max}$ -interval curves. In this example, the second-stage curve drooped at the longest value of  $t_2$ , even though the EDD of the second test systole (half-solid symbol) was greater than the EDD for the previous regular systole. This droop was due not to a decline in contractility but to a fall in aortic diastolic pressure which allowed the aortic valve to open and left ventricular ejection to

begin before the first derivative of pressure could attain its peak isovolumic value,  $P_{max}$ . This blunted the value of  $P_{max}$ . Such blunting generally occurred during the second-stage experiment when  $t_2$  was greater than 600 msec and aortic diastolic pressure was at least 17 mm Hg lower than it was for the previous regular systole. The fall in diastolic aortic pressure that normally occurs between systoles (Fig. 2) continued unabated when the first test systole was ineffective (that is, left ventricular pressure did not rise to a value that opened the aortic valve) until the second test systole. This fall in aortic pressure was altered when the first test systole was able to exceed aortic pressure. The fall in aortic diastolic pressure was greatest when the first test systole was ineffective and  $t_2$  was long.

Figs. 3 and 4 show that the amount of postextrasystolic potentiation depends on  $t_1$ : the shorter  $t_1$ , i.e., the more premature the extrasystole, the greater was the postextrasystolic potentiation (the  $\dot{P}_{max}$ -interval ratio). This was true for almost all the basic intervals tested. The exception occurred when  $t_1$  was so premature that the pressure waveforms of the regular and first test systoles were completely fused. In this case, the value of the  $\dot{P}_{max}$ -interval ratio was smaller than it was for a somewhat longer  $t_1$  for which fusion was partial.

The  $P_{max}$ -interval ratio also depended on the basic interval  $t_0$ . In Fig. 4,  $t_1$  was 205 msec for both second-stage curves, but  $t_0 = 300$  msec for panel A and 350 msec for panel B.  $P_{max}$  of the regular systole was greater at  $t_0 = 300$  msec than at  $t_0 = 350$  msec despite a smaller EDD at the faster rate. (This fall in EDD was seen in all experiments when the basic pacing rate was increased; the faster the rate, the smaller was the EDD.) This enhancement of  $P_{max}$  of the regular systole at the faster rate was greater than the enhancement of the second-stage plateau value. As a result, increasing the rate (with  $t_1$  constant) brought the pleateaus together, thus making the  $P_{max}$ -interval ratio smaller (Fig. 5).

Fig. 5 shows the effect of  $t_1$  on the  $\dot{P}_{max}$ -interval ratio when the heart was paced at basic intervals of 300, 350, and 400 msec. The more premature the test systole, the greater was the  $\dot{P}_{max}$ -interval ratio. As in Fig. 4, A and B, this effect was more pronounced at longer values of  $t_0$ , but, occasionally, as in Fig. 6, the  $\dot{P}_{max}$ -interval ratio curves were the same when the basic intervals were within 50 msec of each other.

### Comment

We have used the isolated muscle and the intact chronically instrumented heart to study the developmental changes in the general characteristics of the force-interval relationship. There are advantages and disadvantages to both preparations.

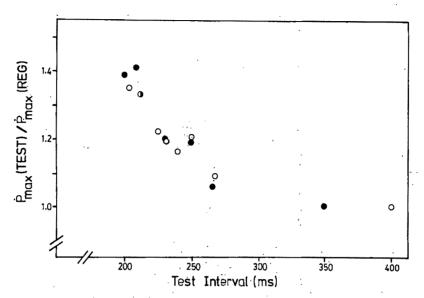


Fig. 6. The P<sub>max</sub>-interval ratio for systoles with the same end-distolic dimension is plotted as a function of the fixed first test interval, t<sub>1</sub> for two different basic pacing intervals: t<sub>0</sub> = 350 msec (solid circles) and to = 400 msec (open circles). The fetus had a gestational age of 139 days, 13 days postoperatively.

The isolated muscle can be held isometric, controlling one of the factors that determine contractility, whereas the volume of the intact ventricle changes continually throughout the cardiac cycle. If the potentiated and regular systoles are to be compared at the same ventricular volume, the interruption in the normal diastolic filling of the ventricle by the first test systole requires that a compensatory pause be introduced after this test systole in order to allow the EDD of the left ventricle to reach that of the previous regular systole. Therefore, it is essential to measure the volume (or the minor axis) of the ventricle, in particularly at end-diastole, so that the changes in Pmax that are due to a change in preload are not mistaken for changes in contractility induced by the force-interval relationship. The apparent absence of the postextrasystolic potentiation from some of the data in Fig. 4 is an example of such a mistake that could only be caught if the enddiastolic dimensions are monitored. Such considerations are especially important for the quantitative evaluation of developmental changes in postextrasystolic potentiation. Earlier studies 16 on the subject need to be repeated while monitoring ventricular volume or end-diastolic dimensions.

The importance of monitoring ventricular dimensions was further emphasized by the spontaneous fluctuations in EDD that occurred in the fetal lamb even when the heart rate was constant. Pmax changed in the same direction as the EDD; thus, the intact fetal heart operates on the ascending limb of the pressure-volume curve. These results are similar to the observations of Kirkpatrick and associates<sup>15</sup> and emphasize that the fetal left ventricle has a significant range of volumes over which it normally operates.

In the isolated preparation, afterload can be considered infinite since the muscle is held isometric. In contrast, in the intact fetal animal, aortic pressure can allow the ventricle to begin ejecting before P<sub>max</sub> is reached; this causes a blunted value of Pmax, as has been described in the adult.<sup>17</sup> Since aortic diastolic pressure continued to decrease as t2 was lengthened, blunting of Pmax could always be seen if t2 was made long enough. This depression of  $P_{max}$  could be mistaken for a decline in contractility, unless aortic pressure (or at least the timing of Pmax with respect to the beginning of ventricular ejection) is also monitored. Incidentally, many of the systoles excluded by this criterion would have been rejected anyway since the ventricle had filled beyond EDD at the basic rate.

In the isolated muscle, the rate and pattern of stimulation can be controlled precisely. The exact values of the test intervals are those at which the test stimuli are applied. In the intact animal, these values must be measured from the electrocardiogram to determine accurately the values of t<sub>1</sub> and t<sub>2</sub>, since the hearts are atrially paced and the characteristics of the atrioventricular system are not constant. A wide range of rates and patterns of stimulation can be used in the isolated muscle, but in the in vivo heart, the ranges of heart rate and prematurity of the first test systole are somewhat restricted by the conduction time and refractory period of the atrioventricular conduction system and ... by the spontaneous rate of the animal: the conduction time can vary not only from beat to beat but also with the prematurity of the test systole—the more premature the test systole, the longer the conduction time. The refractory period of the atrioventricular conduction system in the intact heart places a lower limit on  $t_3$ ,  $t_1$ , and  $t_2$ , whereas the spontaneous rate places an upper limit on  $t_0$ .

In the isolated muscle, the rate of pacing can be slow enough, i.e.,  $t_0$  made long enough (e.g., 3 seconds in this study), to allow contractility ( $\dot{F}_{max}$ ) to develop fully between contractions. In the intact heart, a compensatory pause must be introduced not only for the reasons given above but also to allow contractility ( $\dot{P}_{max}$ ) to reach its plateau value. In addition, the intrinsic heart rate of the lamb varies from day to day, so that a range of  $t_0$  intervals must be obtained on each day of study if data obtained at the same value of  $t_0$  are to be acquired for a significant period of development; consequently, a range of values of  $t_0$  and, in addition,  $t_1$  must be obtained with each study if comparisons are to be made prior to and after experimental interventions from one day to another and from one animal to another.

The basic pacing rate had to be kept low in the isolated muscle because pacing it at the normal rate led to irreversible deterioration in contractility. This loss presumably resulted because diffusion of oxygen from the bathing medium through extracellular space was inadequate at high rates of stimulation. The coronary perfusion of the intact fetal heart would prevent such problems over the range of rates used in this study.

The environment of the isolated muscle can be controlled precisely. In contrast, in the intact animal, the environment of the heart, e.g., concentration of ions or hormones in the blood, is more difficult to control. The sympathetic and parasympathetic tones are even more difficult to control. On the other hand, it is only in studying the response in the intact animal that we can understand how the intact organism is dealing with changes in the environment, such as the increase in concentrations of circulating catecholamines that occurs at birth.<sup>18</sup>

In the isolated muscle studies, different animals must be used to characterize the force-interval relationship at each age. In the chronically instrumented heart, the same animal can be used to measure day-to-day changes in the  $\dot{P}_{max}$ -interval ratio that may take place with development and birth or in the presence of disease.

The results of this study show that the intact animal's force-interval relationship is the same as that of the isolated muscle. This fact, together with the relative ease with which instrumentation of the fetal lamb's

cardiovascular system can be carried out, makes the intact lamb an excellent model for evaluation of the potential changes in the force-interval relationship with development and birth.

The effect of altering the pattern of stimulation on contractility was qualitatively the same in every isolated and intact preparation studied throughout the range of development evaluated, from 93 days' gestation to the adult. The ability of the heart to generate force or pressure after a contraction was depressed shortly after the contraction. When the heart was stimulated to contract at longer and longer times after the previous contraction, the greater was the ability of the heart to generate force or pressure until a plateau of contractility was reached. In both preparations,  $\dot{P}_{max}$  or  $\dot{F}_{max}$  always increased to a plateau with increasing test intervals of t<sub>1</sub> or t2. Postextrasystolic potentiation, described by the  $\dot{F}_{max}$ -interval or  $\dot{P}_{max}$ -interval ratio, was always present and always had the same dependency on the test and basic intervals: when the test interval t1 was held constant, the P<sub>max</sub>-interval ratio increased when the basic interval to was increased; when to was held constant, the ratio decreased when t<sub>1</sub> was increased. These are the characteristic features of the force-interval relationship of all mammalian myocardium.19

At no age did we observe the kind of behavior that characterizes amphibian myocardium, P<sub>max</sub> or F<sub>max</sub> decreasing with an increasing time after the previous contraction, that the test contraction was elicited, or the absence of postextrasystolic potentiation. 19 Thus, if the developmental changes in the force-interval relationship recapitulate the phylogenetic ones, they take place earlier than 93 days' gestation in the sheep. The possibility certainly exists that in other mammals (perhaps in animals that are not able to walk or run at birth) such changes might be found if the force-interval relationship was investigated at similar gestational ages. The lack of qualitative changes in the relationship demands that quantitative changes, e.g., the Fmax or Pmax-interval ratio, must be sought if this relationship is to be useful for evaluating developmental changes in contractility.

In subsequent studies, we will use these isolated and intact preparations to determine the effect that changes in the inotropic state and the muscle length has on the force-interval relationship. This is necessary, for, if changes in muscle length altered the relationship quantitatively, it would be impossible to distinguish the interaction of these changes from those that take place with development. Next, with the use of both isolated muscle preparations and the chronically instrumented fetal and newborn animal, we will chart the quantitative changes in the relationship that take place at birth and during development from fetus to adult.

#### REFERENCES

- 1. McPherson, R. A., Kramer, M. F., Covell, J. W., and Friedman, W. F.: A comparison of the active stiffness of fetal and adult cardiac muscle, Pediatr. Res. 10:660, 1976.
- Friedman, W. F.: The intrinsic physiologic properties of the developing heart, in Friedman, W. F., Lesch, M., and Sonnenblick, E. H., editors: Neonatal Heart Disease, New York, 1973, Grune & Stratton, Inc., pp. 21-49.
- 3. Legato, M. J.: Ultrastructural changes during normal growth in the dog and rat ventricular myofiber, in Lieberman, M., and Sano, T., editors: Developmental and Physiological Correlates of Cardiac Muscle, vol. 1, New York, 1976, Raven Press, pp. 249-273.
- 4. Page, E., Earley, J., and Power, B.: Normal growth of ultrastructures in rat left ventricular myocardial cells, Circ. Res. (Suppl. II) 34 & 35:12, 1974.
- 5. Anderson, P. A. W., Manring, A., and Johnson, E. A.: The force of contraction of isolated papillary muscle. A study of the interaction of its determining factors, J. Cell. Mol. Cardiol. 9:131, 1977.
- 6. Anderson, P. A. W., Rankin, J. S., Arentzen, C. F., Anderson, R. W., and Johnson, E. A.: Evaluation of the force-frequency relationship as a descriptor of the inotropic state of canine left ventricular myocardium, Circ. Res. 39:832, 1976.
- 7. Anderson, P. A. W., Manring, A., Arentzen, C. E., Rankin, J. S., and Johnson, E. A.: Pressure-induced hypertrophy of cat right ventricle: An evaluation with the force-interval relationship, Circ. Res. 41:582, 1977.
- 8. Anderson, P. A. W., Manring, A., Serwer, G. A., Benson, D. W., Edwards, S. B., Armstrong, B. E., Sterba, R., and Floyd, R. D., IV: The force-interval relationship of the human left ventricle, Circulation 60:334, 1979.
- 9. Kirkpatrick, S. E., Naliboff, J., Pitlick, P. T., and Friedman, W. F.: Influence of poststimulation potentiation and heart rate on the fetal lamb heart, Am. J. Physiol. 229:318, 1975.

- 10. Davies, P., Dewar, J., Tynan, M., and Ward, P.: Post-natal developmental changes in length-tension relationship of cat papillary muscle, J. Physiol. (Lond.) 253:95, 1975.
- 1. Krebs, H. A., and Henseleit, K.: Untersuchungen über die Harnstoff Bildung im Tierkoper, Hoppe Seylers Z. Physiol. Chem. 210:33, 1932.
- 2. Meschia, G., Cotter, J. R., Breathnach, C. S., and Barron, D. H.: The diffusibility of oxygen across the sheep placenta, Q. J. Exp. Physiol. 50:466, 1965.
- 13. Comline, R. S., and Silver, M.: Daily changes in foetal and maternal blood of conscious pregnant ewes with catheters in umbilical and uterine vessels, J. Physiol. 209:567, 1970.
- 14. Kirkpatrick, S. F., Covell, J. W., and Friedman, W. F.: A new technique for the continuous assessment of fetal and neonatal cardiac performance, Am. J. OBSTET. GYNECOL. 116:963, 1973.
- 15. Kirkpatrick, S. E., Pitlick, P. T., Naliboff, J., and Friedman, W. F.: Frank-Starling relationship as an important determinant of fetal cardiac output, Am. J. Physiol.
- 16. Arcilla, R. A., Lind, J., Zetterquist, P., Oh, W., and Gessner, I. H.: Hemodynamic features of extrasystoles in
- newborn and older infants, Am. J. Cardiol. 18:191, 1966.
  17. Wallace, A. G., Skinner, N. S., Jr., and Mitchell, F. J.: Hemodynamic determinants of the maximum rate of rise
- of left ventricular pressure, Am. J. Physiol. 205:30, 1963.
  18. Eliot, R. J., Klein, A. H., Glatz, T. H., Lom, R., Nathanielez, P. W., and Fisher, D. A.: Norepinephrine, epinephrine and dopamine responses to parturition in premature and full term fetal sheep, Pediatr. Res. 13:357. 1979.
- 19. Anderson, P. A. W., Manring, A., Sommer, J. R., and Johnson, E. A.: Cardiac muscle: An attempt to relate structure to function, J. Mol. Cell. Cardiol. 8:123, 1976.

### Biophysics of the developing heart

## II. The interaction of the force-interval relationship with inotropic state and muscle length (preload)

PAGE A. W. ANDERSON\* ANDRÉS MANRING CARLYLE CRENSHAW, JR.

Durham, North Carolina

The interaction of the force-interval relationship, muscle length (ventricular volume), and inotropy was evaluated in isolated fetal myocardial preparations and in the in utero chronically instrumented fetal lamb. In the isolated muscle, 93 to 141 days' gestation, a change in muscle length strengthened all contractions equally (multiplicatively) but produced no other changes in either the quantitative or the qualitative characteristics of the force-interval relationship; it was significantly altered by isoproterenol. Similarly, in the intact fetal lamb the qualitative and quantitative features of the relationship did not depend on ventricular volume, e.g., postextrasystolic potentiation was constant over a wide range of volumes. But isoproterenol produced a decrease in postextrasystolic potentiation. These results demonstrate that the force-interval relationship satisfies two major criteria for an index of cardiac contractility and suggest that the relationship may provide a basis for the evaluation of changes in contractility with development and birth. (Am. J. Obstet. Gynecol. 138:44, 1980.)

A WIDE VARIETY of descriptors of cardiac contractility has been evaluated to determine whether they fulfill the necessary criteria for an index of cardiac contractility: (1) independent of heart volume or muscle length, (2) sensitive to changes in the inotropic state, and (3) reflective of sarcomere movement. In the adult heart, in which many indices of cardiac contractility have been evaluated, <sup>1-8</sup> the force-interval relationship has been the only descriptor of the heart's ability to generate force or shortening that has been found to fulfill these requirements—the relationship is constant with a change in muscle length, <sup>9</sup> and quantitatively and

From the Duke University Medical Center.

This work was supported in part by National Institutes of Health Grants HL-20749, HL-11307, and HL-18270, and by The National Foundation–March of Dimes.

Received for publication December 26, 1979.

Revised March 7, 1980.

Accepted March 13, 1980.

Reprint requests: Page A. W. Anderson, M.D., Box 3218, Duke University Medical Center, Durham, North Carolina, 27710.

\*Recipient of Research Career Development Award Grant No. HL-00500.

qualitatively altered by changes in the inotropic state (e.g., exposure to ouabain or norepinephrine, the development of hypertrophy, and the presence of the clinical state of heart failure<sup>10–12</sup>) and sarcomere shortening in the postextrasystolic contraction differs in amount and character from that of the previous regular contraction.<sup>18</sup>

The characteristics of the force-interval relationship have been described in fetal, neonatal, and adult hearts. 14-16 Although its qualitative characteristics have been shown to be the same throughout these stages of development, 16 quantitative differences in response to paired pacing have been reported.14, 15 If, in the fetal and developing heart, the force-interval relationship is to be the basis of a useful descriptor of the developmental changes in cardiac contractility, quantitative changes in the relationship must be shown to result only from changes in inotropy and not from changes in ventricular volume or muscle length. For if the characteristic used to measure contractility depends on ventricular volume, then changes in volume with growth or birth will obscure the description of how contractility changes with these processes.

In the present study, both the isolated muscle preparation from the fetal lamb heart and the chronically

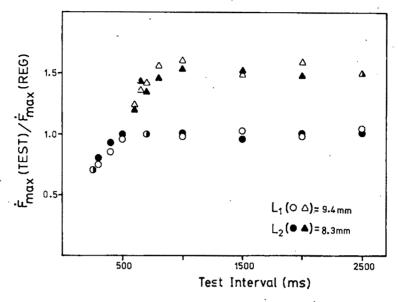


Fig. 1. Effect of muscle length on the normalized force-interval curves.  $\dot{F}_{max}$  of the test contraction divided by  $\dot{F}_{max}$  of the previous regular contraction is described as a function of the test interval,  $t_1$  or t<sub>2</sub>, for an isolated moderator muscle bundle from a fetal lamb at 136 days' gestation. The first-stage results are circles, and the second-stage results are triangles. The curves were obtained at two different muscle lengths: the longer length,  $L_1$  (open symbols) and the shorter length,  $L_2$  (solid symbols). Basic pacing interval, t<sub>0</sub> = 3,000 msec, and for the second-stage curve the fixed first test interval,  $t_1 = 275$  msec.

instrumented, intact fetal lamb in utero will be used to describe the interaction of inotropy, preload, and the rate and pattern of stimulation. This interaction must be known if this relationship is to be used to describe changes in contractility in the developing and newborn animal. The demonstration that the force-interval relationship in the developing heart is sensitive to changes in inotropy, yet unaltered by changes in ventricular volume or muscle length, provides, in subsequent articles, the basis for our description of how contractility changes in the developing fetal and neonatal heart and the subsequent changes in contractility that occur with birth. Potentially, the force-interval relationship may become more valuable as a descriptor of changes in contractility in the developing heart than any other descriptor presently available.

### Methods

Isolated muscle preparation. Trabeculae carneae cordis,  $N^{\bullet}=5$ , or moderator muscle bundle, N=7, was obtained from the right or left ventricle of a fetal lamb (N = 12) of known gestational age (93 to 142 days) from mixed-breed ewes, as previously described.16 The bath, details of the preparation and sacrifice, mounting of the tissue, the method of stimulation, and the processing of the force signal were described previously.11 The peak force and  $\dot{F}_{max}$  of the regular and test contractions (see below) and the time of the occurrence of these values, together with the timing of the test stimulus relative to the previous regular stimulus, were determined.

Force-interval relationship: Experimental procedure. The pacing protocol for the isolated muscle experiments were described previously.16 Briefly, a two-stage experiment (the results are illustrated in Fig. 1) was performed by pacing the muscle at a constant rate of 0.33 hertz. Two test stimuli were interpolated periodically, between every eighth and ninth stimuli at the basic rate. The intervals between the first and second test stimuli and the previous regular stimulus, t1 and t2, were varied systematically in two stages. During the first stage of the experiment, t<sub>2</sub> was fixed at 2,700 milliseconds and t<sub>1</sub> was varied between 275 msec and 2,500 msec.  $\dot{F}_{max}$  of the contractions elicited by the first test stimuli was plotted as a function of t<sub>1</sub> (Fig. 1). During the second stage of the experiment, t<sub>1</sub> was held fixed, e.g., 300, 400, or 500 msec; for each fixed value of t1, t2 was varied between  $t_1 + 300$  msec and 2,500 msec.  $\dot{F}_{max}$ of the second test contraction was plotted as a function of t2 (Fig. 1).

An abbreviated version of the two-stage experiment that allows postextrasystolic potentiation to be monitored and repetitively evaluated was used to test for the effects of a change in length or inotropic state on the force-interval relationship. Two test stimuli were interpolated between the eighth and ninth stimuli at the . "

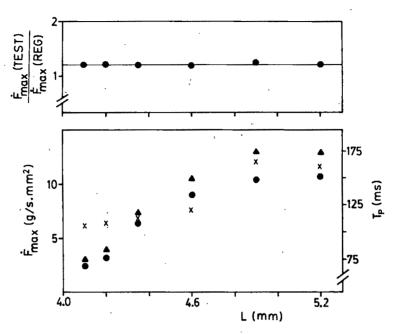


Fig. 2. The upper panel describes the  $F_{max}$ -interval ratio ( $F_{max}$  of the potentiated test contraction,  $F_{max}$  of the potential test contraction, an extrasystole,  $F_{max}$  of the previous regular contraction) as a function of muscle length for an isolated trabeculae carneae from a fetal lamb, 126 days' gestation. The lower panel provides the ralues of  $F_{max}$  for the test contractions (triangles) and the previous regular contractions (triangles). The time to peak force for the previous regular contraction,  $F_{max}$  is also plotted as a function of muscle length.

basic pacing frequency,  $t_0 = 0.33$  Hz. The first test stimulus was applied at a fixed test stimulus interval, e.g.,  $t_1 = 300$  msec, and the second test stimulus was applied at a fixed test stimulus interval,  $t_2 = 2,500$ msec. Postextrasystolic potentiation was described by obtaining a ratio of Fmax of the potentiated beat (the second test contraction) to Fmax of the previous regular beat. The repetitive measurement of this  $\dot{F}_{max}$  interval ratio allowed frequent updating of the effect of isoproterenol or a change in muscle length on the forceinterval relationship. Test stimulus intervals that produced a marked fusion (when the test contraction interrupted the relaxation phase of the previous regular contraction's waveform at 20% or more of peak force) of the first test contraction and the previous regular contraction were avoided.

Effect of length change on the force-interval relationship. After a 2-hour equilibration period at L<sub>max</sub>, the aforementioned two-stage experiment was performed. The muscle length was then shortened. After a 45-minute equilibration period, the two-stage experiment was repeated at the new length. The responses at the two muscle lengths were compared in order to determine whether the shapes of the force-interval curves obtained with the first and second stages of the experiment were the same at the two lengths, i.e., whether

every point on the curve was scaled upward or downward by the same amount (Fig. 1). This comparison was performed by normalizing the test  $\dot{F}_{max}$  with respect to  $\dot{F}_{max}$  of the preceding regular contraction. The effects of the Frank-Starling relationship on the values of  $\dot{F}_{max}$  at the two lengths were thus eliminated. The shape of the curves were then compared by plotting the ratio of  $\dot{F}_{max}$  of the test contraction to  $\dot{F}_{max}$  of the previous regular contraction as a function of the test stimulus intervals,  $t_1$  or  $t_2$ .

The  $\dot{F}_{max}$ -interval ratio obtained from the abbreviated experiment was used to monitor the effect of multiple muscle lengths on the force-interval relationship (see above,  $t_0$ ,  $t_1$ , and  $t_2$  were held constant), as the muscle was shortened and then on return to  $L_{max}$  (Fig. 2). The  $\dot{F}_{max}$ -interval ratio was plotted as a function of muscle length. The paired t test was used to test for significance, p < 0.05 being significant.

Effect of isoproterenol on the force-interval relationship. The muscle was exposed to Krebs-Hensleit solution<sup>17</sup> which contained isoproterenol (10<sup>-8</sup>, 10<sup>-7</sup>, or 10<sup>1-6</sup>M) and ascorbic acid (200 milligrams per liter, added to retard oxidation of isoproterenol). The two-stage experiment and the abbreviated version of the experiment were performed prior to and during a 15-minute exposure of the muscle to isoproterenol.

The abbreviated experiment was repeated continually until the response of the muscle, Fmax, had reached its maximum value. The two-stage experiment was then performed. In some preparations this peak response to isoproterenol fell toward the control value within 1 to 8 minutes: in such preparations the results of the twostage experiment could not be used to construct a force-interval curve because they were obtained during a nonsteady state. After exposure to isoproterenol, the muscle was returned to the Krebs-Hensleit solution for 30 minutes to allow return to the control state. This return to the control state was determined by continued repetition of the abbreviated experiment to monitor the Fmax-interval ratio. The shapes of the force-interval curves and the values of the Fmax-interval ratios were compared in the presence and absence of isoproterenol. A paired t test was used to test for significance, p < 0.05 being significant.

Intact animal preparation. Fetal lambs, N = 7, from age-dated singleton pregnancies (119 to 132 days' gestation) in mixed-breed ewes, underwent instrumentation of their cardiovascular system as previously described.16 This chronic instrumentation of the fetus allowed monitoring of the left ventricular pressure and its first derivative, left ventricular minor axis dimension, superior vena caval pressure, left atrial pressure, intrapleural pressure, intra-amniotic pressure, systemic arterial pressure, and the electrocardiogram. The atrial and vena caval catheters were used to infuse volumes of Normosol or solutions of isoproterenol. Atrial pacing wires allowed the rate and pattern of cardiac contraction to be controlled.

Daily, after the surgical procedure, the ewe was placed in a rolling cage that contained hay and alfalfa pellets and was taken into the laboratory, where she stood facing the sheep in the adjoining room. The instrumentation leads and catheters were attached to the physiologic recording system. Three or more days of this familiarization was performed before the experiments were begun. By that time, the fetal arterial blood gas values, heart rate, and left ventricular pressure were in the range of normal for chronically instrumented in utero lambs;18, 19 as previously described.16

Pacing protocol. The two-stage experimental pacing protocol for the intact animal was modified from the in vitro one. The heart rate was controlled by atrial pacing at an overall rate sufficient to control the lamb's heart rate. Every fifteenth beat at the regular pacing rate was followed by a pause, during which two test stimuli were introduced. Although the timing of the test stimuli (defined above) applied to the atrium was known, the variability of atrioventricular conduction time denanded that we define for the intact animal experiments  $t_1$  and  $t_2$ ; the intervals between the appropriate QRS complexes. The first test contraction was introduced at a fixed value of t<sub>1</sub>. These pacing patterns were applied during the interpolated pause to allow sufficent time for potentiation of P<sub>max</sub> (i.e., postextrasystolic potentiation) of the second test contraction to fully develop and to provide sufficient time for the left vencricular end-diastolic dimension (EDD) to reach a value equal to the EDD of the previous regular systole.16

The complete two-stage experiment was not performed in the evaluation of the effects of a change in EDD or an infusion of isoproterenol on the forceinterval relationship because the indirect or Frank-Starling effects on Pmax produced by the alterations in ventricular filling resulted in smaller values of Pmax for the test systoles with the shortest values of t<sub>1</sub> or t<sub>2</sub>. We Took this effect into account by choosing t2 such that the EDD of the potentiated systole was equal to that of the previous regular systole. This pattern of stimulation was similar to the abbreviated isolated muscle experiment used to evaluate the effect of isoproterenol or a change in muscle length on the force-interval relationship. Since t<sub>2</sub> was chosen so that the postextrasystolic systole (second test systole) and the previous regular systole had equal values of EDD, the Pmax-interval ratio (Pmax of the potentiated systole divided by Pmax of the previous regular one) was unaltered by Frank-Starling effects. Such Pmax-interval ratio values were used to evaluate the response of the in vivo heart to a change in ventricular volume or exposure to isoproterenol.

Effects of ventricular volume. The effects of ventricular volume on the P<sub>max</sub>-interval ratio in the heart of the intact lamb were evaluated by performing the abbreviated experiment as the ventricular volume went from one level of EDD to another by: (1) infusion of prewarmed Normosol, pH 7.4, 5 to 15 ml/kg, into the superior vena cava over 5 to 10 minutes, (2) infusion of prewarmed Normosol, 5 to 10 ml into the left atrium over 2 to 3 seconds, or (3) the spontaneous changes in ventricular volume that occurred naturally while the fetal lamb was being monitored. The Pmax-interval ratio was plotted as a function of the EDD. Paired t testing was carried out to determine significance, p < 0.05 being significant.

Effects of isoproterenol. The Pmax-interval ratio was monitored during the steady state prior to an infusion of isoproterenol and during the infusion. Isoproterenol, 0.0025 to 0.08  $\mu$ g/kg/min was infused for 5 to 20 minutes, and the P<sub>max</sub>-interval ratio was sampled. Because tachycardia was induced by the higher doses of isoproterenol, the basic pacing interval,  $t_0 = 300$ msec, was always used. Paired t testing was per- . "

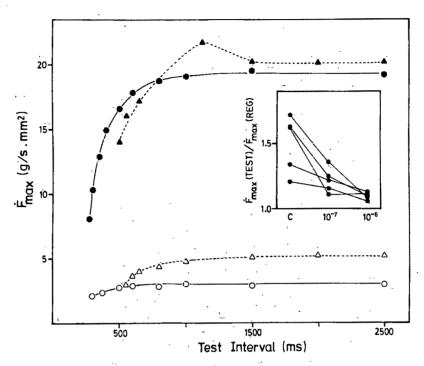


Fig. 3. The force-interval curves in the presence of isoproterenol,  $10^{-6}$ M, (solid symbols) are compared to the curves obtained in the absence of isoproterenol (open symbols). The first-stage curves are circles, and the second-stage curves are triangles;  $t_0 = 3,000$  msec, and for the second-stage experiments,  $t_1 = 300$  msec. Inset: Comparison of the  $F_{mex}$ -interval ratio ( $t_1 = 275$  msec,  $t_2 = 2,500$  msec) in the control solution (C) to the ratio in  $10^{-6}$ M and  $10^{-7}$ M isoproterenol for five fetal muscles, gestational age 130 to 135 days.

formed to determine significance, p < 0.05 being significant.

#### Results

### Isolated muscle.

Effects of muscle length. The contractile response was more stable for the trabeculae carneae than for the moderator muscle bundles. The response of the trabeculae, usually, reached a steady state within 1 hour to 1½ hours of being mounted in the tissue bath, whereas moderator muscles would demonstrate, occasionally, a 10% to 20% hour-to-hour decrease in peak force. Since the complete two-stage experiment required 8 to 15 minutes to complete, such a decline would significantly alter the shapes of the force-interval curves. In contrast, the F<sub>max</sub>-interval ratio (which was sampled every 30 seconds) remained unaltered during these changes in force and Fmax. Consequently, the results of the two-stage experiments were normalized by dividing  $F_{max}$  of the test contraction by  $F_{max}$  of the previous regular contraction. All of these normalized values can be termed a Fmax-interval ratio; unless otherwise specified, we used the term when a second-stage plateau was used to obtain the ratio.

The qualitative characteristics of the force-interval

relationship were the same at all muscle lengths. Fig. 1 illustrates the normalized force-interval curves obtained at two muscle lengths from a moderator muscle bundle taken from the fetal lamb (136 days' gestation). For the contraction at the shortest value of  $t_1$ ,  $\dot{F}_{max}$  had its smallest value, i.e., the ratio of test to regular F<sub>max</sub> had its smallest value. Then as t<sub>1</sub> was increased, F<sub>max</sub> rose monotonically to a plateau equal to Fmax of the previous regular contraction—the normalized value reached 1. In the second-stage results, Fmax of the second test contraction had its smallest value with the shortest t2 and rose monotonically to a plateau that was greater than F<sub>max</sub> of the previous regular contraction. Thus, the ratio exceeded 1, demonstrating postextrasystolic potentiation. The shorter the fixed value of t<sub>1</sub> for the second-stage experiment, the higher was the second-stage plateau, and thus the larger was the Fmaxinterval ratio, that is, the more premature the extrasystole, the greater was the postextrasystolic potentiation. These general characteristics of the force-interval relationship were present at all muscle lengths examined.

A change in muscle length changed the magnitude of  $F_{max}$  but not the shapes of the first-stage and second-stage curves. Thus, both the qualitative and quantitative characteristics of the relationship were un-

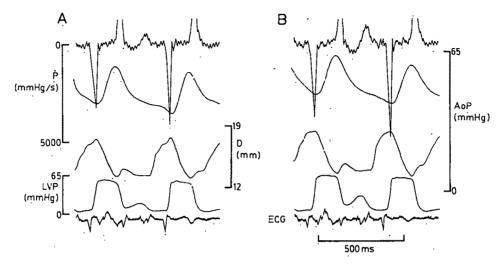


Fig. 4. The effect of heart size on postextrasystolic potentiation ( $t_0 = 300 \text{ msec}$ ,  $t_1 = 205 \text{ msec}$ ). The fetal lamb was at 138 days' gestation, instrumented 16 days previously. A, Control state. B, The results of the same stimulus pattern in the same lamb on the same day after infusion of prewarmed Normosol into the left atrium. The tracing, from top to bottom, are the following: P, first derivative of pressure; AoP, aortic pressure; D, left ventricular minor axis dimension; ECG, electrocardiogram.

changed by a change in muscle length. This is seen in Fig. 1, in which the set of curves obtained at one muscle length is superimposed on the set obtained at the other length, and is further demonstrated by the results of the abbreviated experiment (Methods) carried out at multiple muscle lengths (Fig. 2). No difference was found in postextrasystolic potentiation or the Fmaxinterval ratio over the range of muscle lengths tested. The quantitative characteristics of the force-interval relationship were independent of muscle length, that is, apart from a length-dependent scaling factor, the force-interval curves were the same at every muscle length. This was not true when peak force was used rather than F<sub>max</sub> because the time to peak force depended on muscle length (Fig. 2).

Effect of isoproterenol. When the fetal muscle was exposed to isoproterenol,  $F_{max}$  and  $\overline{F}$  increased, and the quantitative features of the force-interval relationship changed. This was different from the response to a change in muscle length. Fig. 3 illustrates the results of a two-stage experiment obtained from a trabeculae carneae, 132 days' gestation, in the presence and absence of isoproterenol. The slope of the initial portions of both the first-stage and second-stage curves was increased in the presence of isoproterenol, and the plateaus and the curves were brought closer together. There was a suggestion of a qualitative change in the second-stage curve of this fetal lamb since the curve appeared to be biphasic;  $F_{max}$  increased up to  $t_2 =$ 1,200 msec and then fell to a lower plateau with an increase in t2. A similar but much more prominent effect of isoproterenol was found in adult myocardium.10

The effects of isoproterenol as described by the abbreviated experiment are illustrated in the inset of Fig. 3. In all five fetal muscles, the Fmax-interval ratio fell significantly, p < 0.001, with exposure to  $10^{-7}$ M isoproterenol, and this fall was increased further with exposure to  $10^{-6}$ M.

The results show that an alteration in the inotropic state changes the force-interval relationship and does not simply scale it like a change of muscle length.

### Intact animal.

Effect of volume. The effect of volume could not be evaluated over the complete range of values of t<sub>1</sub> and t<sub>2</sub>. This inability was due to the effect of these perturbations in pacing on Pmax that were separate from the force-interval relationship. When a two-stage experiment pacing protocol was performed, a wide variation in EDD resulted, since ventricular filling is dependent on t1 and t2. Since Pmax depends on ventricular filling (see below and Frank-Starling effect), only systoles with the same EDD could be compared. This limited the evaluation of the effect of volume on the force-interval relationship to the plateau portion of the second-stage curves, where EDD of the test systole equaled EDD of the previous regular systole, and Pmax of the previous regular systole.

In Fig. 4, ventricular volume was changed by an infusion of prewarmed Normosol into the left atrium. There was postextrasystolic potentiation in P<sub>max</sub> and in the extent and rate of minor axis shortening at the two values of EDD in A and B of Fig. 4 (fetal lamb, 138 days' gestation instrumented 16 days previously). After the infusion, the systole at the regular rate demonstrated

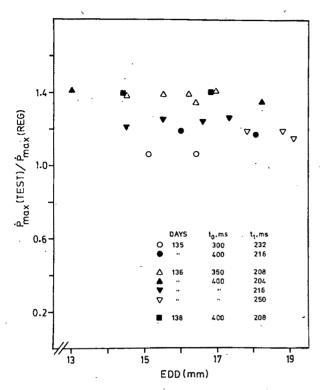


Fig. 5. The effect of left ventricular end-diastolic dimension (EDD) on the Pmax-interval ratio (Pmax of the second test contraction divided by Pmax of the previous regular contraction. both systoles with the same EDD). The ratios obtained at several EDDs for each pacing interval are compared for a fetal lamb instrumented at 132 days' gestation. The symbols indicate the day of gestation, the basic pacing interval (t<sub>0</sub>), and the timing of the fixed first test interval (t1).

an increase in Pmax (from 2,400 to 2,800 millimeters of mercury per second), the aortic peak systolic pressure (40 to 43 mm Hg), and the diastolic pressure (33 to 36 mm Hg). The total amount that the minor axis dimension shortened during systole also increased when the ventricular volume was increased, e.g., in this fetus at a larger volume the dimension shortened form 20.1 mm to 10.5 mm, whereas at a smaller volume it shortened from 15.5 mm to 9 mm (a shortening of 9.6 mm versus 6.5 mm). An ejection phase index, the percent fractional shortening (the end-diastolic dimension minus the end-systolic dimension divided by the end-diastolic dimension),12 was greatest when EDD was largest.

An increase in EDD had similar effects on the regular and test systoles. In particular, the enhancement of P<sub>max</sub> by an increase in volume was the same for every systole. Thus, the Pmax-interval ratio was unchanged by the volume infusion.

Fig. 5 further illustrates this constancy of P<sub>max</sub>interval ratios with changes in EDD. Of course, the ratio depends strongly on the basic pacing rates (1/t<sub>0</sub>) and the test stimulus interval  $(t_1)^{16}$ ; but when the same to and t<sub>1</sub> were used, the P<sub>max</sub>-interval ratio was not significantly different at different values of EDD. Note the large range of values of EDD (13 mm to 18.5 mm) used to test for volume dependence of the forceinterval relationship in this lamb. These results were true throughout the range of gestational ages evaluated. The data in Fig. 5, for example, were obtained from a fetal lamb at three different gestational ages.

Effect of isoproterenol. Fig. 6 illustrates the results of the abbreviated experiment, obtained from a fetal lamb (139 days' gestation instrumented 17 days previously), prior to (panel A) and during (panel B) an infusion of  $0.02 \,\mu g/kg/min$  of isoproterenol. The infusion caused striking changes in ventricular systolic characteristics at the basic pacing rate, in particular an increase in P<sub>max</sub>. The rates of ventricular ejection and diastolic filling were usually increased when isoproterenol was infused. At high doses of isoproterenol, peak arterial pressure usually increased by 4 to 8 mm Hg over control values, and EDD significantly increased (e.g., from 16 to 19 mm), despite an enhancement of minor axis shortening. However, the results in Fig. 6 were chosen to illustrate the effects of isoproterenol because (in this animal and at this dose) the EDD was unchanged and the systolic and diastolic arterial pressures changed by only a few millimeters of mercury. Consequently, the increase in Pmax and the rate of minor axis systolic shortening reflect an enhancement in contractility induced by isoproterenol and not indirect effects of changes in ventricular volume or aortic pressure. However, the postextrasystolic potentiation in Pmax and the amount and rate of minor axis systolic shortening were abolished by isoproterenol. Indeed, there was postextrasystolic depression (i.e., the ratio was less than unity). This decrease in postextrasystolic potentiation—to the point of depression-induced by isoproterenol was found in all the fetal animals studied. In addition, this alteration in postextrasystolic potentiation induced by isoproterenol was not altered by an increase in EDD.

Fig. 7 illustrates the effects of isoproterenol on the P<sub>max</sub>-interval ratio of six fetal lambs. Note the prominent fall in the ratio in the presence of isoproterenol. The effect of three different concentrations of isoproterenol on the Pmax-interval ratio for one lamb is also shown in Fig. 7: the higher the infusion rate, the lower was the  $\dot{P}_{max}$ -interval ratio.

In summary, these results, like those for the isolated muscle preparation, demonstrated that the forceinterval relationship and the effects of changing ventricular volume interact in a multiplicative or scaling way to alter P<sub>max</sub>, but that the force-interval relation-

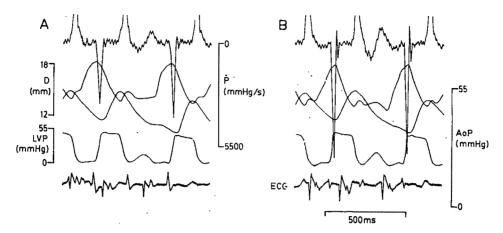


Fig. 6. The effect of isoproterenol on the response to an extrasystole ( $t_0 = 300$  msec,  $t_1 = 210$  msec) for a fetal lamb 139 days' gestation instrumented 17 days previously. A, Control state. B, The response in the same lamb on the same day to an infusion of isoproterenol, 0.02 µg/kg/min. The tracings from top to bottom are the following: P, first derivative of pressure; D, left ventricular minor axis dimension; AoP, aortic pressure, LVP, left vent-icular pressure; ECG, electrocardiogram.

ship and an alteration in the inotropic state (isoproterenol) interact in a more complex manner. Thus, the P<sub>max</sub>-interval ratio reveals changes in the inotropic state, regardless of the superimposed changes in volume.

#### Comment

Our previous evaluations of the dependence of contractility on the rate and pattern of contraction in both the developing and adult hearts demonstrated that the qualitative aspects of the relationship were unchanged over a broad developmental range, which extended in the sheep from 93 days' gestation to adulthood. 16 The curves were always monotonic, and there was always postextrasystolic potentiation. Consequently, developmental changes in the force-interval relationship, if they occurred, would be quantitative ones, such as the amount of postextrasystolic potentiation. As in the adult animal, quantitative characteristics of the forceinterval relationship, e.g., postextrasystolic potentiation, depended on the basic rate, 1/t<sub>0</sub>, and on the prematurity of the extrasystole (first test contraction), t<sub>1</sub>: when to was held constant and to increased, postextrasystolic potentiation decreased; when t<sub>1</sub> was held constant and to decreased, postextrasystolic potentiation decreased.11. 12. 16, 20

It is clear that to and to should be standardized if quantitative results at different developmental ages are to be compared. Unfortunately, standardization has not been used in previous studies describing developmental changes, e.g., the response to paired pacing was measured in one study by means of the shortest possible coupling interval, 15 and in another by means of

the interval that produced the greatest amount of potentiation.14

The findings in these studies may not reflect developmental changes in the force-interval relationship so much as developmental changes in the refractory period or the duration of the action potential. Certainly, in view of the dependency of potentiation on t<sub>0</sub> and t<sub>1</sub>, these intervals must be the same if the extent of potentiation is to be compared from one age to another.

Of course, standardization of the rate and pattern of stimulation would only be sufficient to characterize the developmental changes if, as we demonstrate in this study, the  $\dot{F}_{max}$  or  $\dot{P}_{max}$ -interval ratio is independent of length or ventricular volume. Otherwise, the experimenter would not know whether his results reflect a developmental difference in postextrasystolic potentiation or merely a difference in ventricular volume. If the studies were carried out in the intact fetal animal, in which the daily increases in ventricular volume and the acute increase with birth cannot be controlled, the effects of postextrasystolic potentiation and volume on the quantitative characteristics of the force-interval relationship would not have been separable.

The present study describes how the pattern of stimulation and the muscle length interact to produce changes in contractility, e.g., Pmax or Fmax. In the isolated muscle experiments, changes in length altered the magnitude of contractility according to the Frank-Starling law of the heart (Fig. 2) but had no effect on the force-interval ratio. In Fig. 1, the monotonic rising phases of both the first-stage and second-stage curves obtained at the two lengths were superimposed, and demonstrate that both the qualitative and quanti-

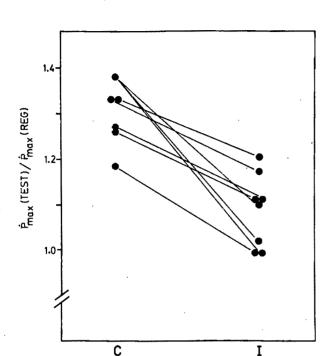


Fig. 7. The effect of isoproterenol on the  $P_{\text{max}}$ -interval ratio is described for six fetal lambs. The solid circles above C were obtained in the control state, in the absence of isoproterenol; those in the presence of isoproterenol are above the I. The three lines leaving from the top circle indicate the responses of one lamb to three different doses of isoproterenol. The higher the infusion dose, the lower was the ratio.

tative characteristics of the relationship are unaltered by a change in length. The constancy of the quantitative characteristics is also shown by the finding that the  $F_{max}$ -interval ratio was the same at multiple muscle lengths (Fig. 2).

Thus, in the isolated muscle preparation, the characteristics of the force-interval relationship were unaffected by a change in muscle length. But would this also hold true for the more complex preparation, the intact heart of the chronically instrumented fetal lamb in utero? In the intact animal, other descriptors of contractility do not lend themselves easily to describing only changes in inotropy. Pmax is not a satisfactory descriptor, because as Kirkpatrick and associates21 showed and as this study confirmed, Pmax increased with an increase in end-diastolic dimension. Not only was P<sub>max</sub> enhanced by an increaseed in end-diastolic dimension, but an ejection phase descriptor of contractility, percent fractional shortening, was greater at larger end-diastolic dimensions. These results demonstrate that, in the fetal lamb, the Frank-Starling relationship is operational in the range of ventricular volumes for which we studied our fetal animals. These results are similar to those of Kirkpatrick and associates21 and contrary to the conclusion by Heymann and Rudolph<sup>22</sup> that the Frank-Starling relationship is largely inoperative in the fetal lamb. Their demonstration that stroke volume increased only a small amount with a large increase in atrial pressure does not prove this conclusion. Those findings must be coupled with the in vitro and in vivo muscle studies that demonstrate low compliance of fetal muscle.23, 24 Since the in vivo ventricular volume loading experiments of Heymann and Rudolph were not performed so that the ventricular volume could be monitored, there might have been only small changes in end-diastolic volume with the large changes in end-diastolic pressure. When the volume dependence of the fetal lamb was evaluated by Kirkpatrick and associates<sup>21</sup> during the monitoring of left ventricular end-diastolic dimension in the chronically instrumented preparation, they noticed a constant and significant increase in stroke volume with an increase in end-diastolic dimension over a physiologic range of end-diastolic pressures.

We attempted to study the effect on Pmax of the interaction of the force-interval relationship with volume over as large a range as possible, since the changes in ventricular volume that occur with birth are so large and so acute that they may change the Pmax-interval ratio. If this were so, then changes in Pmax in the perinatal period might reflect changes produced by alterations in ventricular volume and inotropy that are expressed by changes in the Pmax-interval ratio in such an inextricable fashion that true changes in contractility would not be recognized. The range of EDD in which the P<sub>max</sub>-interval ratio was examined was so large (Fig. 5) that it overlapped the range of EDD that occurs after birth, as previously described25 and as we will illustrate in subsequent reports. These results, like those in the isolated muscle, demonstrate that the Pmax-interval ratio, a quantitative descriptor of the force-interval relationship, is unaltered by large increases in ventricular volume and the associated large increases in  $P_{max}$  (Figs. 4 and 5).

The ability to separate the effects of the force-interval relationship on  $\dot{P}_{max}$  and  $F_{max}$  from those of length reassured us that the force-interval relationship could be used as a basis for an index of contractility. However, potentiation of these values might also have been unaltered by inotropic changes, which would have made the index relatively useless. The likelihood that the  $\dot{P}_{max}$  or  $\dot{F}_{max}$ -interval ratio is altered by inotropic interventions is not only likely but may be of aid in distinguishing how various inotropic agents alter cardiac contractility from one developmental stage to another. For example, norepinephrine produces postex-

trasystolic depression in older puppies but enhances postextrasystolic potentiation in younger puppies. 26 To test for such dependency of the force-interval relationship, a positive inotropic agent, isoproterenol, was used to induce inotropic change in both the isolated preparation and the intact heart preparation. In both, the quantitative characteristics of the force-interval relationship (e.g., the  $\dot{F}_{max}$ -interval or  $P_{max}$ -interval ratio) changes in the same direction with exposure to isoproterenol. In both, isoproterenol decreased the P<sub>max</sub> or F<sub>max</sub>-interval ratio. The higher the concentration of isoproterenol, the greater the decrease in these ratios. Although the changes in the intact animal in the presence of isoproterenol were revealed when the aortic diastolic pressure and end-diastolic pressure remained unchanged, these changes were also unaffected by changes in EDD, as might be expected, and by increases of 3 to 10 mm Hg in aortic diastolic pressure. (The increase in EDD noted during the infusion of isoproterenol may have represented a decrease in pulmonary vascular resistance that resulted in an increased pulmonary venous return and a larger left ventricular volume.27)

These responses to isoproterenol suggest that the way n which  $\beta$  agonists alter contractility at different developmental stages may provide insight into their mode of action. Furthermore, the effect of disease, e.g., congenital cardiovascular lesions, or perinatal stres on the force-interval relationship may be used to understand how contractility in the developing heart is altered acutely and chronically by pathologic processes. This potential use is suggested by previous studies on the force-interval relationship of children that showed quantitative and qualitative differences between norma children and children with left ventricular hypætrophy or failure.12

Subsequent studies will utilize the force-interval relatorship to describe how cardiac contractility is altered during development over the last third of gestation and through the first few months of life and to describe and analyze acute changes in contractility that occur after birth and compare these changes to other cerdiovascular characteristics in the intact lamb.

### REFERENCES

- 1. Frank, O.: Zur Dynamik des Herz muskels, Z. Biol.
- 2. Starling, E. H.: The Linacre Lecture on the Law of the Heart (Cambridge, 1915, monograph), London, 1918, Longmans, Green.
- 3. Lundin, G.: Mechanical properties of cardiac muscle, Acta Physiol. Scand (Suppl) 20:1, 1944.
- 4. Parmley, W. W., Chuck, L., and Sonnenblick, E. H.: Relation of  $V_{max}$  to different models of cardiac muscle, Circ. Res. 30:34, 1972.
- 5. Benzing, G., III. Stockert, J., Nane, E., and Kaplan, S.: Evaluation of left ventricular performance; circumferential fiber shortening and tension, Circulation 49:925,
- 6. Hirshleifer, J., Crawford, M., O'Rourke, R. A., and Karliner, J. S.: Influence of acute alterations in heart rate and systemic arterial pressure on echocardiographic measures of left ventricular performance in normal human subjects, Circulation **52:**835, 1975.
- 7. Rankin, L. S., Moos, S., and Grossman, W.: Alterations in preload and ejection phase indices of left ventricular performance, Circulation 51:910, 1975.
- 8. Quinones, M. A., Gaasch, W. H., and Alexander, J. K.: Influence of acute changes in preload, afterload, contractile state and heart rate on ejection and isovolumic indices of myocardial contractility in man, Circulation **53:**293, 1976.
- 9. Anderson, P. A. W., Manring, A., and Johnson, E. A.: Force-frequency relationship: a new index of cardiac contractility? Circ. Res. 33:665, 1973.
- 10. Anderson, P. A. W., Manring, A., and Johnson, E. A.: The force of contraction of isolated papillary muscle; a study of the interaction of its determining factors, J. Cell. Mol. Cardiol. 9:131, 1977.

- Anderson, P. A. W., Manring, A., Arentzen, C. E., Ran-kin, J. S., and Johnson, E. A.: Pressure-induced hy-pertrophy of cat right ventricle: An evaluation with the force-interval relationship, Circ. Res. 41:582, 1977.
- 12. Anderson, P. A. W., Manring, A., Serwer, G. A., Benson, D. W., Edwards, S. B., Armstrong, B. E., Sterba, R., and Floyd, R. D., IV: The force-interval relationship of the left ventricle, Circulation 60:334, 1979.
- .3. Manring, A., Beall, H. C., Anderson, P. A. W., and Johnson, E. A.: The force-frequency relationship and sarcomere motion-frequency relationship in cardiac muscle, J. Gen. Physiol. 64:6A, 1974.
- 14. Davies, P., Dewar, J., Tynan, M., and Ward, P.: Post-natal developmental changes in length-tension relationship of cat papillary muscle, J. Physiol. (Lond.) 253:95, 1975.
- 12 Kirkpatrick, S. E., Naliboff, J., Pitlick, P. T., and Friedman, W. F.: Influence of post-stimulation potentiation and heart rate on the fetal lamb heart, Am. J. Physiol. 229:318, 1975.
- 16. Anderson, P. A. W., Manring, A., and Crenshaw, C., Jr.: Biophysics of the developing heart. I. The force-interval relationship, Am. J. OBSTET. GYNECOL. 138:33, 1980.
- .7. Krebs, H. A., and Henseleit, K.: Untersuchungen über die Harnstoff Bildung im Tierkoper, Hoppe Seylers Z. Physiol. Chem. 210:33, 1932.
- 18. Meschia, G., Cotter, J. R., Breathnach, C. S., and Barron, D. H.: The diffusibility of oxygen across the sheep placenta, Q. J. Exp. Physiol. 50:466, 1965.
- 19. Comline, R. S., and Silver, M.: Daily changes in foetal and maternal blood of conscious pregnant ewes with catheters in umbilical and uterine vessels, J. Physiol. 209:567, 1970.
- Arentzen, C. E., Rankin, J. S., Anderson, P. A. W., Feezor, M. D., and Anderson, R. W.: Force-frequency characteristics of the left ventricle in the conscious dog. Circ. Res. 42:64, 1978.

- Kirkpatrick, S. E., Pitlick, P. T., Naliboff, J., and Friedman, W. F.: Frank-Starling relationship as an important determinant of fetal cardiac output, Am. J. Physiol. 231:495, 1976.
- 22. Heymann, M. A., and Rudolph, A. M.: Effects of increasing preload on right ventricular output in fetal lambs in utero, Circulation 48:(Suppl. 4): 37, 1973.
- 23. Friedman, W. F.: The intrinsic physiologic properties of the developing heart, Prog. Cardiovasc. Dis. 15:87, 1972.
- 24. Friedman, W. F.: The intrinsic physiologic properties of the developing heart, in Friedman, W. F., Lesch, M., and
- Sonnenblick, E. H., editors: Neonatal Heart Disease, New York, 1973, Grune & Stratton, Inc., pp. 21-49.
- Kirkpatrick, S. E., Covell, J. W., and Friedman, W. F.: A new technique for the continuous assessment of fetal and neonatal cardiac performance, Am. J. Obstet. Gynecol. 116:963, 1973.
- Anderson, P. A. W., Manring, A., and Nassar, R.: Developmental changes in cardiac contractility, Pediatr. Res. 13:339, 1979.
- 27. Rudolph, A. M.: Fetal and neonatal pulmonary circulation, Annu. Rev. Physiol. p. 383, 1979.

### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following written statement, signed by one author: "The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C. V. Mosby Company in the event the work is published. The undersigned author warrants that the article is original, is not under consideration by another journal, and has not been previously published. I sign for and accept responsibility for releasing this material on behalf of any and all co-authors." Authors will be consulted, when possible, regarding republication of their material.

# Midtrimester abortion induced by hyperosmolar urea and prostaglandin $F_{2\alpha}$ in patients with previous cesarean section: Clinical course and potential for uterine rupture

MILAGROS F. ATIENZA, M.D.
RONALD T. BURKMAN, M.D.
THEODORE M. KING, M.D., Ph.D.
Baltimore, Maryland

Reviewed was the clinical course of 76 patients with a hearry of previous cesarean section from among 1,626 patients undergoing midtrimester abortion. Educed with intra-amniotic hyperosmolar urea and prostaglandin  $F_{2\alpha}$ . The cesarean section group had long injection-abortion intervals, more frequently received additional oxytocin for augmentation and more frequently experienced incomplete abortion. Also, one patient experienced a uterne rupture. A review of the literature dealing with uterine rupture subsequent to induced middimester abortion revealed that the typical patient was older and multiparous, had an injection-abortion interval of more than 24 hours, and had received intravenous oxytocin continuously for more than 12 hours. Although there has been no previous report of a uterine rupture with midtrimester abortion in patients who have undergone a prior cesarean section, because of the present findings such patients require careful monitoring and the judicious use of oxytocic agents. (Am. J. Obstet. Genecol. 138:55, 1980.)

THE UTILIZATION of cesarean section for the management of obstetric problems has shown a gradual increase in the United States over the past several years. The factors responsible for such increased use were reviewed recently. Therefore, in many institutions, the frequency of cesarean section per number of live births approaches or even exceeds 20%.

During the same period of time, although the percentage of patients in the United States who requested midtrimester termination of pregnancy gradually declined to approximately 9% in 1977,<sup>2</sup> the absolute number of patients presenting in the midtrimester dic not appreciably change during the past several years. Therefore, there will be a number of patients requesting midtrimester termination who have undergone a

From the Fertility Control Center, Department of Gynecology and Obstetrics, The Johns Hopkins Medical Institutions.

Received for publication December 4, 1979. Revised February 25, 1980. Accepted March 27, 1980.

Reprint requests: Milagros F. Atienza, M.D., Departmer t of Gynecology and Obstetrics, Harvey-309, 600 North Wolfe St., Baltimore, Maryland 21205.

prior cesarean section. This article describes the experience at the Fertility Control Center of The Johns Hopkins Hospital with the management of such patients, and also presents a case report of uterine rupture after midtrimester amnioinfusion in a patient who had previously undergone a cesarean section.

### Material and methods

Midtrimester terminations of pregnancy in the Fertility Control Center have been carried out on patients presenting between 16 and 22 weeks from the first day of the last menstrual period. Most of the patients in the Center have been managed by the intra-amniotic injection of hyperosmolar urea, augmented with either intra-amniotic prostaglandin  $F_{2\alpha}$  (PGF<sub>2\alpha</sub>) or intravenous oxytocin, or both. For the purpose of this review, only cases were included in which intra-amniotic PGF<sub>2\alpha</sub> was used initially for augmentation in doses of 10 and 5 milligrams, since such cases represented over 70% of the midtrimester amnioinfusions completed between October, 1972, and June, 1979.

Detailed methodology with regard to the use of hyperosmolar urea for midtrimester abortion has been the subject of previous reports.<sup>3-5</sup> After removal of approximately 200 milliliters of fluid at amniocentesis,

	No.		n-abortion val (hr)
		Mean	Range
Ürea + PGF <sub>2α</sub> (10 mg), no			
laminaria tent			•
No prior cesarean section			
Para 0	624	15.9	2-60
Para 1 or more	425	13.8	1-47
Previous cesarean section	34	17.2	3-40
Urea + $PGF_{2\alpha}$ (5 mg), no		•	•
laminaria tent		-	
No prior cesarean section		•	
Para 0	213	17.0	6-45
Para I or more	107	14.7	3-46
Previous cesarean section	26	23.4	8-40
Urea + PGF <sub>2α</sub> (5 mg), one			-
laminaria tent		•	•
No prior cesarean section			
Para 0	160	12.7	4-46
Para 1 or more	21	14.4	4-45
Previous cesarean section	16	15.1	2-38

<sup>\*</sup>From intra-amniotic injection of medication to abortion of the fetus.

**Table II.** Injection-abortion intervals\* greater than 24 hours

-	Ņo.	Patients with injection-abortion intervals greater than 24 hr		
		No.	%	
Urea + PGF <sub>2α</sub> (10 mg), no			,	
laminaria tent				
No prior cesarean section	1,049		12.9	
Previous cesarean section	34	12	35.3	
Urea + $PGF_{2\alpha}$ (5 mg), no laminaria tent	• •			
No prior cesarean section	320	48	15.0	
Previous cesarean section	26	14	53.8	
Urea + PGF <sub>2α</sub> (5 mg), one laminaria tent		•		
No prior cesarean section	181	13	7.2	
Previous cesarean section	16	6	37.5	

<sup>\*</sup>From intra-amniotic injection of medication to abortion of the fetus.

135 ml of a 59.7% solution of urea is slowly infused via gravity. Immediately after the infusion of urea,  $PGF_{2\alpha}$  in a dose of either 10 or 5 mg is injected intraamniotically. The lower dose of  $PGF_{2\alpha}$  is used because research efforts have defined it as the minimally effective dose which still maintains an injection-abortion interval consistently less than 24 hours. In addition, recent efforts to reduce the frequency of cervical injury have led to the intracervical placement of one or more laminaria tents for 4 to 6 hours prior to infusion of urea. Only patients in whom one laminaria tent was

placed are included in this review, since there were insufficient numbers of patients with more than one laminaria tent to be useful for analyses. Intravenous oxytocin at a rate of 332 mU per minute is also employed for three indications: failure to abort within 24 hours after infusion of urea when there is no evidence of labor; absence of labor 4 hours after rupture of membranes; and management of incomplete abortion.

In the Fertility Control Center, failed abortion is defined as the requirement for vaginal evacuation of the products of conception at 48 hours, or sooner in instances of suspected chorioamnionitis or significant hemorrhage. Incomplete abortion is defined as failure to pass all or part of the placenta within 2 hours after abortion of the fetus. Such patients are managed by ring forceps curettage with intravenous analgesia of meperidine and diazepam.

For the purpose of this review, patients with a history of prior cesarean section who underwent amnioinfusion of urea, augmented with either 10 or 5 mg of  $PGF_{2\alpha}$ , were compared with the general group of patients at the Fertility Control Center in whom this methodology was employed. Factors examined included clinical characteristics of the patients, outcome, injection-abortion intervals, requirements for oxytocin, and complications. When appropriate, the means and standard errors of the means were calculated, and these data were analyzed by an F test and Student's t test in order to determine statistical significance.

### Results

There were 1,083 patients who underwent infusion of hyperosmolar urea and  $PGF_{2\alpha}$  (10 mg) without the use of laminaria tents, 346 patients who received urea and  $PGF_{2\alpha}$  (5 mg) without the use of laminaria tents, and 197 patients who received urea and  $PGF_{2\alpha}$  (5 mg) plus the intracervical insertion of one laminaria tent before the injection. The frequencies of prior cesarean section among patients in the three groups were, respectively, 3.1%, 7.5%, and 8.1%.

A review of the clinical characteristics of the various study groups showed some differences. The average age of patients presenting to the Fertility Control Center for the urea method of abortion was 20.5 years, whereas patients with a previous history of cesarean section were about 2 years older. All patients with a history of prior cesarean section had been delivered of a fetus beyond 24 weeks' gestation. In contrast, between 42 and 46% of all Fertility Control Center patients in the groups studied were para 0 at presentation for abortion. The mean duration of gestation at the time of injection ranged between 19 and 20 weeks from the first day of the last menstrual period, and an aver-

Table III. Outcome

, ,		Complete aborticn		Incomplete abortion		Failure	
	No.	No.	7%	No.	. %	No.	%
Urea × PGF <sub>2α</sub> (10 mg), no laminaria tent				• •	-		
No prior cesarean section	1,049	551	52.5	482	46.0	16	1.5
Previous cesarean section	34	. 15	44.1	18	47.0	1	2.9
Urea + $PGF_{2\alpha}$ (5 mg), no				•	•		
laminaria tent	.•	•					
No prior cesarean section	320	208	€5.0	110	34.4	. 2	0.6
Previous cesarean section	26	11	£2.4	14	53.8	1	3.8
Urea + $PGF_{2\alpha}$ (5 mg), one laminaria tent						_	
No prior cesarean section	181	130	71.8	49	27.1	2	1.1
Previous cesarean section	16	10	32.5	6	37.5	0	_

age of between 195 and 210 ml of amniotic fluid was removed at the time of amniocentesis. No important differences were discernible between the various groups studied and prior cesarean section patients versus other patients for these two characteristics.

Table I lists the injection-abortion intervals for the various groups in the review. As shown, the injectionabortion intervals of patients with a history of a previous cesarean section were consistently longer than those of any of the other groups of patients. The difference between patients who were para 1 or more and those with prior cesarean section in the group given urea plus PGF<sub>2α</sub> (5 mg) with no laminaria tent was statistically significant (p < 0.05), but similar comparisons in the other groups were not significant. In addition, the preinjection use of a laminaria tent appeared to have only a modest effect in reducing the mean injection-abortion interval of patients who had previously had a cesarean section.

Table II compares the injection-abortion intervals exceeding 24 hours among the various study groups. As demonstrated in the table, patients with a history of prior cesarean section had a high proportion of injection-abortion intervals that exceeded 24 hours. Therefore, such patients also had a greater requirement for additional augmentation with oxytocin according to the protocol followed in the Fertility Control Center. An examination of the groups given urea plus  $PGF_{2\alpha}$  (10 mg) and urea plus  $PGF_{2\alpha}$  (5 mg) with no laminaria tent showed that the percentages of patients without a previous cesarean section not receiving oxytocin during their hospital admission were 32.1 and 29.3, respectively. In contrast, only 20.6% and 11.9% of the patients with a history of previous cesarean section in each of those same groups did not receive oxytocin during the course of their hospital admission.

Table III details the clinical outcome in the various study groups. Although few differences were noted in

the groups of patients given urea plus  $PGF_{2\alpha}$  (10 mg), the rate of incomplete abortion for patients with previous cesarean section was consistently higher in the groups of patients given urea plus  $PGF_{2\alpha}$  (5 mg) regardless of whether a laminaria tent was employed.

In a comparison of the complications encountered by patients with previous cesarean section versus other patients in the study groups, no significant differences were discernible among the groups in rates of hemorrhage, infection, cervical laceration, and gastrointestinal problems. These complications have been presented and discussed in detail previously.3-5 However, one patient with a history of a previous cesarean section in the group given urea plus  $PGF_{2\alpha}$  (5 mg) without a laminaria tent experienced a uterine rupture. Her clinical course is summarized below.

### Case report

This 32-year-old patient, para 5, presented for termination of pregnancy at 18 weeks from the first day of her last menstrual period. Her obstetric history was significant in that, after four spontaneous vaginal deliveries, her last delivery (12 years ago) had been effected by cesarean section because of premature rupture of the membranes. Preoperative physical examination and laboratory studies gave findings that were within normal limits, except for an enlargement of the uterus to 18 weeks in size.

Clinical course. An intra-amniotic injection of 135 ml of 59.7% urea and 5 mg of PGF2c was completed without incident on the day of hospital admission. After 24 hours of regular uterine contractions, the cervix was partially effaced and dilated 2 cm. Infusion of oxytocin at 332 milliunits per minute was started, but the cervix remained unchanged at 31 hours after intra-amniotic injection. At 37 hours, the patient complained of generalized myalgia associated with increasing pain in the left lower quadrant of the abdomen. The vital signs revealed a temperature of 100.2° F, blood pressure of 118/80 mm Hg, and a pulse rate of 132 beats per minute. Examination of the abdomen demonstrated diffuse tenderness and guarding in both the right and left lower quadrants, with exquisite pain elicited by palpation of the left flank. Pelvic examination disclosed a brownish discharge emerging from the cervix, which was high in the vagina and displaced to the right. Bimanual examination confirmed the existence of tenderness and guarding in both lower abdominal quadrants, and deviation of the uterine fundus toward the right lower abdomen; an ill-defined mass filled the left lower quadrant. The clinical impression was that of uterine rupture with intra-abdominal expulsion of the products of gestation, and an associated hematoma of the left pelvic wall.

Exploratory laparotomy revealed that the left broad ligament was displaced by a large hematoma of approximately 1,500 ml. A uterine laceration about 5 cm in length was located at the left lateral aspect of the previous transverse uterine cesarean section scar, and the laceration extended into the left broad ligament. The placenta and fetus were protruding from the laceration into the left posterior pelvis. A supracervical hysterectomy was completed, along with excision of the left fallopian tube and ovary and drainage of the hematoma. About 2,000 ml of blood was lost during the operation, and hemostasis was achieved with difficulty, so that the patient required seven units of whole blood and two units of fresh frozen plasma.

The postoperative course of the patient was complicated by the need for two additional units of blood, persistent ileus that required treatment with a long intestinal tube, and fever. However, she was discharged from the hospital on the seventeenth postoperative day in good condition.

### Comment

There are some interesting facets to this review of patients with a history of previous cesarean section who presented to the Fertility Control Center for subsequent midtrimester termination of pregnancy via intra-amniotic instillation of hyperosmolar urea. The frequency of previous cesarean section as a pre-existing medical condition appears to parallel the increasing use of cesarean section in obstetric practice. Therefore, one might predict that, unless the requirement for secondtrimester abortion procedures declines, those who provide abortions will see an increasing number of patients who present with this condition. The review also indicated that patients with a history of previous cesarean section had long injection-abortion intervals, more frequently received additional oxytocin for augmentation of labor, and more frequently experienced incomplete abortion. In addition, the pre-injection use of a laminaria tent did not markedly improve matters, although injection-abortion intervals were shortened somewhat. Therefore, such patients may be at increased risk for uterine rupture unless the use of oxytocic drugs is judiciously monitored. Similarly, because of this potential risk of uterine rupture, the attempt to shorten the injection-abortion interval to less than 24 hours consistently with the use of oxytocic drugs in high doses may be inappropriate for the management of such patients. Unfortunately, because of the numbers involved, we cannot determine whether the described case of uterine rupture in a patient with a previous cesarean section represents an unusually high incidence of this complication.

Six cases of uterine rupture associated with induced midtrimester abortions have been reported previously, but none of the patients had undergone any previous uterine operation. The abortifacients employed included intra-amniotic hypertonic saline,  $PGF_{2\alpha}$ , and, in one instance, 40% urea. In two of the reported cases, death occurred as a result of a delay in diagnosis before the required definitive operation was carried out. All reported cases were unaborted for 24 or more hours after intra-amniotic injection; and in all, large quantities of oxytocin were given continuously for more than 12 hours. Three of the six patients were over 30 years of age, and all were multiparous, para 2 or greater.

The patient reported on here had many of the characteristics of patients who experience uterine rupture associated with induced midtrimester abortion. These characteristics included age, multiparity, prolonged injection-abortion interval, and continuous use of intravenous oxytocin for more than 12 hours. In addition, this patient had a history of prior delivery of an infant by cesarean section (12 years earlier).

In regard to the location of the uterine laceration, in the previous case reports, five of the six uterine ruptures involved the lower uterine segment. These lacerations were usually vertical, not uncommonly in the lateral aspect of the uterus, and were associated with the development of hematomas of the broad ligaments, with expulsion of the products of gestation either into the peritoneal cavity or into the retroperitoneal space. In patients with a history of prior uterine operations, one would anticipate rupture of the uterine scar, as was observed in the current case.

The symptomatology of patients with uterine rupture in this situation includes increased or constant pelvic and abdominal pain and tenderness in the flanks, particularly with an associated ascending retroperitoneal dissection of an enlarging pelvic hematoma. The commonly observed clinical signs include guarding, rebound tenderness, suggestion of more than one pelvic mass, and tachycardia. Delay in recognizing the significance of these findings can result in a catas-

trophic outcome. The prompt recognition of the signs and symptoms of uterine rupture in the currently reported case allowed definitive surgical therapy prior to shock.

At this point, the proper approach to termination of a midtrimester pregnancy in patients who have had previous cesarean sections or prior uterine operations has not been adequately defined. However, our opinion is that such patients constitute a high-risk group which requires careful monitoring and the judicious use of oxytocic drugs. In addition, the pre-injection use of laminaria tents may offer some, although not complete, protection against the possibility of uterine rupture.

#### REFERENCES

- 1. Mann, L. I., and Gallant, J.: Modern indications for cesarean section, Am. J. Obstet. Gynecol. 135:437, 1979.
- Abortion Surveillance-United States, 1977, Morbid. Mortal. Weekly Rep. 28:381, 1979.
- 3. Burkman, R. T., Atienza, M. F., King, T. M., et al.: Intra-amniotic urea and prostaglandin F2a for midtrimester abortion: A modified regimen, Am. J. OBSTET. Gynecol. 126:328, 1976.
- 4. King, T. M., Dubin, N. H., Atienza, M. F., et al.: Intraamniotic urea and prostaglandin  $F_{2\alpha}$  for midtrimester abortion: Clinical and laboratory evaluation, Am. J. OBSTET. GYNECOL. 129:817, 1977.
- 5. Burkman, R. T., Atienza, M. F., King, T. M., et al: Hyperosmolar urea for elective midtrimester abortion: Experience in 1,913 cases, Am. J. OBSTET. GYNECOL. 131:10,

- 6. Horwitz, D. A.: Uterine rupture following attempted saline abortion with oxytocin in a grandmultiparous patient, Obstet. Gynecol. 43:921, 1974.
- 7. Hayashi, R. H., Rothwell, R. O., and Weinberg, P. C.: Uterine rupture complicating midtrimester abortion in a young woman of low parity, Int. J. Gynaecol. Obstet. 13:229, 1975.
- 8. Propping, D., Stubblefield, P. G., Golub, J., and Zuckerman, J.: Uterine rupture following midtrimester abortion by laminaria, prostaglandin  $F_{2\alpha}$ , and oxytocin: Report of two cases, Am. J. Obstet. Gynecol. 128:689, 1977.
- 9. Grimes, D. A., Cates, W., Pettitti, D. B., and Pakter, J.: Fatal uterine rupture during oxytocin-augmented, saline-induced abortion, Am. J. OBSTET. GYNECOL. 130:

# Umbilical blood flow response to embolization of the uterine circulation

JAMES F. CLAPP III, M.D.
HAZEL H. SZETO, M.D., PH.D.
RODNEY LARROW
JEAN HEWITT
LEON I. MANN, M.D.
Burlington, Vermont

The uterine and umbilical blood flow response to uteroplacental insufficiency, produced by microsphere embolization of the uteroplacental circulation, was examined by means of electromagnetic flow transducers in 12 pregnant ewes. No acute changes were observed in either circulation immediately after embolization of the uterine vasculature. Significant morphometric fetal growth retardation, in terms of weight, length, and ponderal index, was not associated with early changes in fetal pH, Po<sub>2</sub>, or Pco<sub>2</sub>. However, the incremental increases in both flows that were observed in control animals did not occur either during or after embolization because of an increase in vascular resistance. During and after embolization the incremental increase in uterine blood flow was blunted or decreased in most, but not all, animals. A rapid, progressive, and persistent decrease in umbilical flow occurred in the growth-retarded group. The significance of these findings relative to intrauterine growth is discussed. (Am. J. Obstet. Gynecol. 138:60, 1980.)

IN THE PREGNANT ewe, the rate of uterine and umbilical blood flow progressively increases with advancing gestation and fetal growth.<sup>1, 2</sup> Both follow a circadian pattern and are reciprocally related to one another over a 24-hour interval.<sup>3</sup> However, in chronically instrumented ewes, acute reduction in the rate of uterine flow produces either no change<sup>4-6</sup> or a slight decrease<sup>6-8</sup> in the rate of umbilical blood flow.

Although the effects of a chronic reduction in uterine perfusion on fetal growth are well documented, its effect on the rate of umbilical blood flow has been reported only by Creasy and associates. Using a microsphere technique, they observed a reduction in both the absolute and relative rate of umbilical flow at term

• From the Department of Obstetrics and Gynecology, University of Vermont College of Medicine.

Supported by National Institutes of Health Grants RCDA No. 5 KO4 HD00213-02 and No. 5 RO1 HD11122-02.

Received for publication November 8, 1979.

Revised March 4, 1980.

Accepted March 27, 1980.

Reprint requests: James F. Clapp III, M.D., Given Medical Building C 217, University of Vermont College of Medicine, Burlington, Vermont 05401.

after embolization of the uterine circulation earlier in gestation. This was not associated with a change in fetal arterial pressure, which suggests that the observed redistribution of cardiac output was related to a change in either umbilical or systemic vascular resistance, or both.

The present series of experiments was designed to sequentially examine the umbilical and uterine circulatory response before, during, and after a period in which the uterine circulation was repetitively embolized, in order to determine the time course and etiology of the flow response.

### Material and methods

Animal preparation. Fifteen dated ewes with singleton pregnancies were surgically prepared between 110 and 120 days of gestation. Under a combination of spinal and pentobarbital anesthesia, precalibrated Dienco electromagnetic flow transducers were placed, by a retroperitoneal approach, on the main uterine artery that supplied the pregnant horn and on the common umbilical artery. The uterine flow transducer was positioned just distal to the posterior pelvic branch of the internal iliac artery and proximal to the dorsal uterine branch of the main uterine artery. The umbilical

transducer was placed on the common umbilical artery, as originally described by Berman and associates, 10 after ligation of the one anterior and two posterior pelvic branches. Via an arcuate branch, a polyvinyl catheter was advanced in a retrograde fashion until its tip lay in the main uterine artery proximal to the dorsal branch and distal to the uterine artery flow transducer. Additional catheters were placed in the fetal and maternal descending aortas via the femoral artery, the common umbilical vein by transabdominal puncture,11 the main uterine vein of the pregnant horn via a tributary, the amniotic fluid, and maternal inferior vena cava. Solder-ball electrodes were placed extradurally over the right temporoparietal area of the fetal cerebral cortex via burr holes.12 All catheters and leads were brought to the maternal flank, where they were transfixed to the skin or stored in a flexible pouch. Intraoperatively, 1 gram of ampicillin was placed in the amniotic fluid and maternal peritoneal cavity. No preoperative or postoperative antibiotics were used.

Experimental plan. The animals were initially divided into a control (N = 5) and an embolization group (N = 10). With the animals standing quietly in an experimental cart, daily measurements of vascular pressures and flows were obtained over at least a 90-minute interval between 7 and 11 A.M. Mean daily flow rates and pressures were calculated as the average of the means of 6-minute sequential intervals of the record. Both maternal and fetal pH, Po2, and Pco2 were moni-

Beginning on the fourth postoperative day, control measurements were obtained in both groups for 4 or 5 days in order to establish baseline pre-embolization values. Then, in the embolization group, the uterine circulation was embolized with two million 15-micron microspheres at least every other day over an intervalof 4 to 11 days. The decision to stop embolization of the uterine circulation was arbitrary in the initial five animals because we could not attain in our preparation the endpoints established by others.13 In the remainder of the animals, embolization was discontinued when umbilical flow had reached the level observed on the fourth postoperative day. The postembolization period of observation ranged from 4 to 13 days and was terminated either by premature labor or elective delivery between 139 and 142 days' gestation.

At the time of delivery by cesarean section, the placement of flow transducers and catheters was confirmed, the flow transducer calibrations were confirmed, and fetal weight and crown-rump length were obtained. With the use of weight for gestational age, ponderal index, visual soft tissue wasting, and amount

**Table I.** Morphometric parameters

ĭ	Gestational age (days)	Birth weight (kg)	Crown- rump length (cm)
Term lambs	137-142		
Group I $(N = 4)$	139.3	3.68 (0.42)	46.0 (0.4)
Group II $(N = 3)$	139.2	3.76 (0.11)	46.0 (0.6)
Group III $(N = 3)$	138.3	2.46 (0.15)*	43.5 (0.9)*
Premature lambs	130-135		
Group I $(N = 1)$	131	2.86	43.5
Group III $(N = 4)$	131.6	1.89 (0.08)	39.5 (0.3)

Values are expressed as mean. Those in parentheses are the standard error of the mean.

of amniotic and allantoic fluid as indices of intrauterine growth retardation, three of the ten fetuses in the embolization group showed no evidence of growth retardation at term. Therefore, for purposes of analysis, we divided the embolization group into a normally grown (N = 3) and an intrauterine-growth-retarded group (N = 7). Thus, we obtained longitudinal data on three groups of animals: the controls (Group I), the embolized with normally grown fetuses (Group II), and the embolized with growth-retarded fetuses (Group III).

Methodology. Arterial, venous, and amniotic fluid pressures were measured by means of Statham P23 strain gauge transducers coupled to a Beckman RM eight-channel recorder. Maternal zero reference was set at 6 centimeters above the sternum, and amniotic fluid pressure was used as the fetal zero reference. The uterine and umbilical arteriovenous pressure gradients were measured as the difference between maternal or fetal aortic and uterine or umbilical venous pressure. A Radiometer micro blood gas analyzer, calibrated at 38.5° C, was used for determination of Po<sub>2</sub>, and Pco<sub>2</sub>.

Dienco electromagnetic flowmeters coupled to the same recorder were used for all flow measurements. Prior to each implantation, the flow transducers were acutely calibrated on the carotid artery of an intact animal by means of a graduated cylinder and stopwatch over a flow range from 100 to 600 milliliters per minute. At the time of delivery, the uterine flow transducer calibration was verified in situ by a similar technique. Although only the relationship between flow zero and electrical zero was verified in situ for the umbilical flow transducer, its calibration was verified immediately after removal on the maternal carotid artery. In no instance was a discrepancy of more than 5% between pre-implantation and postimplantation calibration values obtained, and the flowmeter output was linear within the range of measurement.

For purposes of statistical analysis, the data were

<sup>\*</sup>Indicates significance at the 0.05 level.

Table II. Fetal effects of uterine embolization

•	Pre-embolization		During embolization		Postembolization				
· ·	Group I	Group II	Group III	Group I	Group II	Group III	Group I	Group II	Group III
рH	7.41	7.41	7.43	7.41	7.39	7.41	7.40	7.40	7.41
	(0.01)	(0.01)	(0.02)	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)	(0.02)
Po <sub>2</sub>	$\hat{\bf 2}2.3$	20.0	21.5	22.9	20.0	21.7	21.9	20.7	18.9*
-	(1.9)	(1.3)	(0.5)	(2.0)	(1.7)	(0.7)	(1.7)	(0.9)	(1.1)
Pco <sub>2</sub>	39.4	39.0	37.9	38.2	$\hat{40.3}^{'}$	38.0	38.8	40.0	40.4
	(0.9)	(1.5)	(1.8)	(1.0)	(0.9)	(1.3)	(1.3)	(1.2)	(2.1)
Arterial pressure	47.8	52.0	46.3	47.2	52.3	47.1	47.8	55.0	50.0
(mm Ĥg)	(2.2)	(3.0)	(1.8)	(2.4)	(2.8)	(1.5)	(2.9)	(2.6)	(1.4)
Umbilical pressure	42.0	44.7	39.6	39.4	45.0	39.8	41.6	47.2	42.5
gradient (mm Hg)	(1.9)	(3.3)	(1.2)	(1.1)	(2.1)	(1.1)	(2.1)	(2.5)	(1.6)

Values are expressed as group mean. Those in parentheses are the standard error of the mean.

Table III. Effect of uterine embolization on umbilical blood flow-Mean daily incremental changes in the absolute rate of umbilical blood flow (flow slope)

	Pre-embolization		During embolization		Postembolization	
	Flow slope (ml min <sup>-1</sup> day <sup>-1</sup> )	Variance	Flow slope (ml min <sup>-1</sup> day <sup>-1</sup> )	Variance	Flow slope (ml min <sup>-1</sup> day <sup>-1</sup> )	Variance
Group I	24.7	14.1	24.4	16.3	24.1	13.6
•	(3.5)	(3.1)	(3.9)	(4.2)	(3.1)	(3.8)
Group II	34.3	166.7	-4.7*†	383.0	2.3‡	672.7
•	(7.4)	(67.8)	(9.7)	(152.6)	(4.6)	(138.7)
Group III	35.2	28.1	-12.3§	22.8	-14.2*8	27.0
4-	(7.3)	(8.0)	$(5.4)^{1}$	(9.3)	(2.0)	(9.8)

Values are expressed as group mean and mean group variances for each study interval. Values in parentheses are standard error of the mean.

grouped into three time intervals (pre-embolization, during embolization, and postembolization) in each of the three groups. The repeated measures test with analysis of variance and the paired t test were used to detect significant changes over time within groups, and analysis of variance and the Scheffe test were used for intergroup comparisons within the same time interval. A p value of less than 0.05 was used to reject the null hypothesis.

Vascular resistance was calculated as the quotient of the pressure gradient and absolute flow rate and expressed in mm Hg ml-1 min-1. Umbilical blood flow per unit weight of fetal tissue was calculated as the quotient of the mean absolute flow rate obtained over the 3-day interval prior to sacrifice and the fetal weight at delivery. The average rate of change in absolute flow rate through the umbilical circulation and main uterine artery was calculated by means of linear regression

analysis and is expressed as the change in absolute flow rate (ml min-1) per day, which is the slope of the regression line calculated from the data.

### Results

The morphometric data obtained at the time of sacrifice is presented in Table I. The 10 term animals either entered spontaneous labor between 137 and 139 days' gestation (N = 4) or were sacrificed prior to the onset of labor between 139 and 142 days' gestation (N = 6). Five animals experienced the spontaneous onset of labor between 130 and 135 days' gestation and were classified as premature.

Seven of the 10 embolized animals were delivered of fetuses with clear evidence of intrauterine growth retardation (Group III). Within this group, the term fetuses were significantly lighter and shorter than those of the nonembolized controls, and the premature

<sup>\*</sup>Indicates significance at the 0.05 level.

<sup>\*</sup>Indicates within-group longitudinal significance at the 0.001 level.

<sup>†</sup>Indicates a significant difference from Group I in the same study interval at the 0.05 level.

<sup>‡</sup>Indicates a significant difference from Group I in the same study interval at the 0.01 level.

<sup>§</sup>Indicates a significant difference from Group I in the same study interval at the 0.001 level.

<sup>|</sup>Indicates within-group longitudinal significance at the 0.01 level.

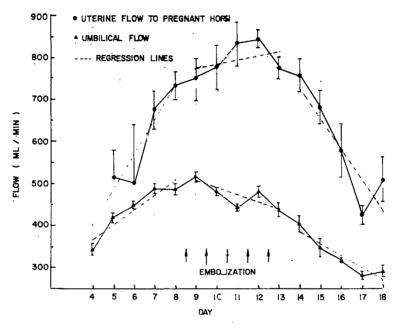


Fig. 1. Ewe No. 268. The flow response to embolization of the uterine circulation as measured in the main uterine artery that supplied the pregnant horn and in the common umbilical artery of the fetus. The fetus was growth retarded at delivery. Each point represents the mean and standard deviation of a 90-minute recording interval. The superimposed broken lines are the regression lines calculated for each period of observation.

fetuses were small for gestational age. All had ponderal indices

$$\left(\frac{\text{Weight (gm)} \times 100}{\text{Crown-rump length (cm)}^3}\right)$$

significantly lower than those obtained in the controls, indicating a more pronounced retardation of soft tissue than axial growth. The fetuses of the three animals comprising Group II were indistinguishable from the controls.

The fetal pH, Po<sub>2</sub>, Pco<sub>2</sub>, and pressure measurements are presented in Table II by study period and group. The observed rate of change in umbilical blood flow is presented in a similar fashion in Table III, and the calculated changes in umbilical vascular resistance appear in Table IV.

During the pre-embolization period of study no significant differences were present between the three groups in fetal arterial pressure, pH, Po<sub>2</sub>, Pco<sub>2</sub>, umbilical pressure gradient, or umbilical vascular resistance. Although no significant differences were present between groups in the daily incremental changes in the rate of umbilical blood flow, a good deal of variability was observed between the individual animals (range, 11 to 74 ml min<sup>-1</sup>day<sup>-1</sup>). However, the individual values were normally distributed about a mean daily incremental increase of  $32 \pm 4$  ml min<sup>-1</sup>day<sup>-1</sup> and were quite constant from day to day for an individual ani-

Table IV. Effect of uterine embolization on umbilical vascular resistance

	Pre- embolization	During embolization	Postembolization
Group I	0.071	0.058*	0.054*
	(0.005)	(0.004)	(0.002)
Group II	0.074	0.079	0.088†
•	(0.015)	(0.017)	(0.008)
Group III	0.097	0.108‡	0.130*§
. •	(0.013)	(0.011)	(0.011)

Values are expressed as the mean group vascular resistance for each study interval in units of mg Hg ml<sup>-1</sup> min. Values in parentheses are standard error of the mean.

\*Indicates within-group longitudinal significance at the 0.05 level.

†Indicates a significant difference from Group I in the same study interval at the 0.05 level.

=Indicates a significant difference from Group I in the same study interval at the 0.01 level.

3 Indicates a significant difference from Group I in the same study interval at the 0.001 level.

mal. The individual consistency in the rate of change in umbilical blood flow over time was striking and is illustrated by the regression lines superimposed on the data in Figs. 1 and 2. In only three animals was significant daily fluctuation observed. In the remainder, the correlation coefficients of the regression lines were 0.850 or greater, and the variances were low, as shown by the

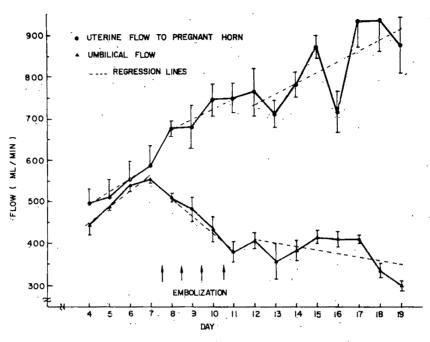


Fig. 2. Ewe No. 208. Data similar to those in Fig. 1, from another animal in Group III. Note the difference in the uterine flow response to embolization.

mean variances for Group I and III in Table II.

The acute effect of injecting microspheres into the uterine circulation was evaluated on twenty-five occasions in the embolized animals. Flow, pressure, and blood gas measurements were obtained before, during, and for 30 minutes after embolization. No consistent acute changes in any parameter were observed. In no instance did flow or resistance change more than  $\pm 5\%$  in either circulation.

During the embolization period, repetitive embolization did not significantly alter fetal pH, Po<sub>2</sub>, or Pco<sub>2</sub> in Groups II and III when compared with either the control animals or the within-group pre-embolization values. Likewise, there was no significant within-group or between-group change in either fetal arterial pressure or the pressure gradient across the umbilical circulation.

Over this time interval, in the control animals, umbilical blood flow continued to increase daily at a rate comparable to that observed in the pre-embolization period. Again, considerable interanimal variability was present, but the value for each individual animal was quite constant and virtually the same as the pre-embolization value. In each of the five animals, the correlation coefficient remained above 0.850, which is reflected by the low mean group variance (Table III). Concurrently, there was a significant decrease in umbilical vascular resistance when compared to the withingroup pre-embolization values (Table IV).

In the embolized animals, repetitive embolization was associated with an abrupt, significant alteration in the rate of change of umbilical blood flow. This is shown graphically for two of the animals from Group III in Figs. 1 and 2. In the three animals of Group II, a mean daily decremental change in umbilical blood flow of 4.7 ml min<sup>-1</sup>day<sup>-1</sup> was observed throughout the period of embolization. This was significantly different from both the mean daily increase of 24.4 ml min<sup>-1</sup> day-1 that occurred in the control animals and the within-group pre-embolization value. However, considerable day-to-day fluctuation in the rate of umbilical blood flow was seen in each of these animals. As a result, the correlation coefficients were less than 0.650, and the mean group variance was high. In the seven animals of Group III, umbilical blood flow decreased at an average rate of 12.3 ml min<sup>-1</sup>day<sup>-1</sup> throughout the embolization period. Again, this was significant when compared to either that in the control animals or to the within-group pre-embolization value but was not significantly different from that in the animals of Group II. Interanimal variability was maintained but, in contrast to the animals in Group II, the daily decremental change was quite constant from day to day for any individual animal. As a result, the correlation coefficients remained high and the mean group variance

The significant decrease in umbilical vascular resistance observed in the control animals did not occur

during the period of embolization in either Group II or Group III. In both, the slight increases which occurred did not attain significance when compared to the preembolization values, but the mean value in Group III was significantly higher than that concurrently obtained in the control group.

During the postembolization period of study, there were no significant differences between the three groups in either fetal pH or Pco2. In Group III, the decrease in fetal Po2 was significant in comparison to the within-group pre-embolization and embolization values and approached significance when compared to the control values. There were no significant withingroup or between-group alterations in either fetal arterial pressure or the pressure gradient across the umbilical circulation.

In the control animals, umbilical blood flow continued to increase at a rate comparable to that observed during the pre-embolization and embolization periods. Again, the day-to-day incremental increase in flow was quite constant for any individual animal, with high correlation coefficients and a low group mean variance. Umbilical vascular resistance remained low. In the three animals of Group II, the day-to-day fluctuation in the rate of umbilical blood flow seen in each of the animals during embolization persisted, with low correlation coefficients and a high group mean variancé. The mean daily increase in the rate of umbilical blood flow of 2.3 ml min<sup>-1</sup>day<sup>-1</sup> was not significantly different from the 4.7 ml min<sup>-1</sup>day<sup>-1</sup> decrease observed during embolization, but it remained significantly different from that observed in the control animals. In the animals of Group III, the changes and consistency observed during embolization persisted throughout the postembolization period. Umbilical blood flow continued to decrease at an average rate cf 14.2 ml min-1day-1, with high correlation coefficients and a low group mean variance. This value remained highly significant both within Group III and in comparison to the controls. Also, during this period of study, it was significantly (0.05) different from that observed in the animals of Group II. Umbilical vascular resistance continued to rise in both Group II and Group III. The between-group comparison indicated that the values obtained in both groups were significantly different from those in the control animals, whereas the withingroup comparison indicated longitudinal significance only in Group III.

Despite the disparity in fetal weight between the groups, umbilical blood flow, expressed as flow per unit weight of fetal tissue, reflected the changes observed in absolute flow. In the animals of Group I, the mean rate of umbilical blood flow was  $254 \pm 28$  ml min<sup>-1</sup>kg<sup>-1</sup>over the last 3 days of study. This value was significantly (0.001) higher than that observed in the animals of Group II  $(177 \pm 4 \text{ ml min}^{-1}\text{kg}^{-1})$  or Group III  $(155 \pm 10 \text{ ml min}^{-1}\text{kg}^{-1})$  over the same period. The latter values were not statistically different from one another.

During the three study periods, no significant alterations occurred in maternal arterial pH, Po2, or Pco2. Maternal mean arterial pressure and the pressure gradient across the uterine circulation slowly decreased in all three groups over time but achieved longitudinal within-group significance at the 0.05 level only in the control animals. There were no significant differences between groups in any study period. In the controls, maternal arterial pressure decreased from a preembolization value of 89.0  $\pm$  4.6 mm Hg to 82.3  $\pm$  4.2 mm Hg in the postembolization period. Over the same interval, the pressure gradient across the uterine circulation decreased from  $78.8 \pm 4.7$  to  $71.7 \pm 4.1$  mm Hg.

In most animals there were wide day-to-day fluctuations in the estimated rate of uterine blood flow. Consequently, the variances were large and, in most instances, the data failed to achieve significance. During the pre-embolization period, no significant differences were present between groups. In Group I, the mean daily increase in uterine flow was  $30.1 \pm 10.8$  ml min<sup>-1</sup>day<sup>-1</sup>, with a mean variance of 114. In Group II, the means were  $37.6 \pm 11.9$  ml min<sup>-1</sup>day<sup>-1</sup> and 698. In Group III, the average daily increase in flow was  $39.3 \pm 12.3$  ml min<sup>-1</sup>day<sup>-1</sup>, and the average variance was 221. During the period of embolization, flow continued to increase in the controls at a mean rate of  $20.8 \pm 8.2$  ml min<sup>-1</sup>day<sup>-1</sup>, with a mean variance of 76. In the embolized animals, the flow response to repetitive embolization was extremely variable from animal tc animal, with no consistent pattern. In Group II, mean values were a daily flow increase of  $33.3 \pm 55.9$ ml min<sup>-1</sup>day<sup>-1</sup>, with a variance of 4,096. In Group III, the mean daily increase in uterine flow fell to  $1.0 \pm 6.7$ ml min-1day-1, with a variance of 74. This change approached, but failed to achieve, significance when compared to either the control group or the withingroup pre-embolization value. In the postembolization period, uterine blood flow continued to rise in the control animals at a mean rate of  $23.6 \pm 12.1$  ml min<sup>-1</sup>day<sup>-1</sup>, with a mean variance of 163. The mean value obtained in the animals of Group II (flow,  $3.5 \pm 15$  ml min<sup>-1</sup>day<sup>-1</sup>; variance, 381) was not significantly different. In Group III, mean uterine flow rate decreased at a rate of 10.8 ± 14.9 ml min<sup>-1</sup>day<sup>-1</sup> over this study period, with a mean variance of 246.

Although statistically significant when compared to that of the control animals, the response was not consistent in all animals (Figs. 1 and 2).

### Comment

The longitudinal data obtained from the control animals in this study demonstrate that the progressive rise in both uterine and umbilical blood flow with advancing gestation<sup>1, 2</sup> is due to a gradual decrease in the vascular resistance of the respective circulations rather than to an increase in the pressure gradient across them. This observation is consistent with continued cotyledonary vascular growth and/or vasodilation in both circulations.<sup>14</sup>

The mean umbilical blood flow per kilogram of fetus in Group I of 254 ± 28 ml min<sup>-1</sup>kg<sup>-1</sup> compares favorably with those values that we have reported<sup>7, 8, 11</sup> with the use of the diffusion equilibrium technique; but is higher than that reported by others who used either flowmeters<sup>4, 10</sup> or microspheres.<sup>9, 10</sup> The reason for this discrepancy is not immediately apparent, since other cardiovascular parameters were similar.<sup>4</sup>

The daily decrease in umbilical blood flow observed during and after microsphere embolization of the uterine vasculature was rapid, consistent, and persistent when associated with intrauterine growth retardation. This was clearly related to a concomitant, progressive increase in umbilical vascular resistance. Although similar data were obtained from the three embolized animals with normally grown fetuses, the changes were blunted, lacked consistency in the individual animal, and were not progressive over time.

The combination of a persistent, progressive decrease in flow secondary to a rising umbilical vascular resistance was the only evidence that we had been successful in producing intrauterine growth retardation. No consistent early changes were observed in other parameters. Despite the rapidity of the umbilical flow response, vascular pressures in both circulations were unchanged. Likewise, pH, Po2, and Pco2 cid not fluctuate from pre-embolization values until the postembolization period, when a decrease in fetal Po2 was observed. These data indicate that, in this species, fetal growth rate is not sensitive to small decreases in Po<sub>2</sub>. Rather, they suggest that fetal growth rate is limited by placental factors other than gas exchange which are more sensitive to vascular compromise. The absence of an early fetal pressor response, fall in Po<sub>2</sub>, or evidence of metabolic acidosis suggests that the fetus rapidly adjusts its metabolic demands to the constraints imposed by these factors, with a resultant reduction in growth rate. The absence of fetal growth retardation in the three animals with a blunted umbilical flow response indicates that an early, consistent, progressive decremental flow response reflects significant compromise of the more sensitive placental factors necessary for maintaining fetal growth rate.

The variability observed in the uterine flow response to embolization was unanticipated and cannot be explained on the basis of the data. Although in many instances the changes in uterine flow paralleled those in the umbilical circulation (Fig. 1), this was not always observed (Fig. 2), and the day-to-day variation was great. Since flow in the contralateral uterine artery was not monitored nor was flow distribution studied, a definitive statement cannot be made. However, the lack of a consistent response suggests that, at a local level, maternal cotyledonary flow may redistribute to preferentially overperfuse undamaged chorionic surface area, and/or maintain perfusion of most tissues through collaterals.

In all probability, the surgical preparation and instrumentation itself had an effect on fetal growth. Our control animals were delivered of lambs which weighed, on an average, 300 grams less than those of minimally instrumented animals in our laboratory, and 800 grams less than those reported by Creasy and associates.9 However, further comparison with the data of the latter authors indicated that the fetal effects of embolization were similar in magnitude. The decrease in fetal weight in the growth-retarded groups was comparable (33% vs. 30%), as was the observed reduction in umbilical blood flow expressed either as total flow (53% vs. 53%) or as flow per kilogram of fetus (39% vs. 32%). Likewise, total umbilical flow in our growth-retarded group at term  $(374 \pm 31 \text{ ml min}^{-1})$ was comparable to theirs (339  $\pm$  28 ml min<sup>-1</sup>). However, flow rates per kilogram of fetus were higher in this series (159 vs. 109 ml min<sup>-1</sup>kg<sup>-1</sup>) since our growth-retarded fetuses were 800 grams lighter.

Error in the measurement of umbilical flow with prolonged transducer implantation is possible but unlikely. All pelvic branches that arose distal to the transducer were ligated at the time of operation. At necropsy, transducer placement was carefully checked, and in no instance was there evidence of angulation or lumenal compromise. Fetal hypertension, a reported effect of lumenal compromise, was not seen. Transducer function was accurately checked both prior to implantation and at the time of sacrifice. No discrepancies were observed.

In summary, the longitudinal data obtained in this study indicate that the progressive increase in uterine and umbilical blood flow observed in the control animals was related to a progressive decrease in the vascular resistance of the respective circulations. Repetitive

embolization of the uterine circulation produced fetal growth retardation only when an abrupt, consistent, and persistent daily decrease in umbilical blood flow occurred as a result of a progressive rise in umbilical vascular resistance. Neither fetal hypertension nor fetal acidosis was observed in the growth-retarded group. A consistent uterine flow response was not observed.

#### REFERENCES

- Rosenfeld, C. R., Morriss, F. H., Makowski, E. L., Meschia, G., and Battaglia, F. C.: Circulatory changes in the reproductive tissues of ewes during pregnancy, Gynecol. Obstet. Invest. 5:252, 1974.
- Rudolph, A. M., and Heymann, M. A.: Circulatory changes during growth in the fetal lamb, Circ. Res. 26:289, 1970.
- Walker, A. M., Oakes, G. K., McLaughlin, M. K., Ehrenkrantz, R. A., Alling, D. W., and Chez, R. A.: 24-Hour rhythms in uterine and umbilical flows of conscious pregnant sheep, Gynecol. Obstet. Invest. 8:288, 1977.
- 4. Berman, W., Goodlin, R. C., Heymann, M. A., and Rudolph, A. M.: Relationships between pressure and flow in the umbilical and uterine circulations of the sheep, Circ. Res. 38:262, 1976.
- Ehrenkrantz, R. A., Walker, A. M., Oakes, G. K., McLaughlin, M. K., and Chez, R. A.: Effect of ritodrine infusion on uterine and umbilical blood flow in pregnant sheep, AM. J. OBSTET. GYNECOL. 126:343, 1976.
- sheep, Am. J. Obstet. Gynecol. 126:343, 1976.
  6. Oakes, G. K., Walker, A. M., Ehrenkrantz, R. A., Cefalo, R. C., and Chez, R. A.: Uteroplacental blood flow during hyperthermia with and without respiratory alkalosis, J. Appl. Physiol. 41:197, 1976.
- Clapp, J. F.: Placental bed blood flow in the pregnant ewe, *m* Chamberlain, G. U. P., and Wilkinson, A. W., editors: Placental Transfer, London, 1979, Pitman Medical, p. 60.
- Clapp, J. F.: Acute exercise stress in the pregnant ewe, Am. J. Obstet. Gynecol. 136:489, 1980.

- Creasy, R. K., DeSwiet, M., Kahanpaa, K. V., Yoong, W. P., and Rudolph, A. M.: Pathophysiological changes in the fetal lamb with growth retardation, in Foetal and Neonatal Physiology, Cambridge, 1973, Cambridge University Press, p. 641.
- Berman, W., Goodlin, R. C., Heymann, M. D., and Rudolph, A. M.: Measurement of umbilical blood flow in fetal lambs in utero, J. Appl. Physiol. 39:1056, 1975.
- Clapp, J. F., Abrams, R. M., and Patel, N.: Fetal metabolism during recovery from surgical stress, Gynecol. Obstet. Invest. 8:299, 1977.
- 12. Mann, L. I., Duchin, S., and Weiss, R. R.: Fetal EEG sleep stages and physiologic variability, Am. J. Obstet. Gynecol. 119:533, 1974.
- 13. Creasy, R. K., Barrett, C. T., DeSwiet, M., Kahanpaa, K. V., and Rudolph, A. M.: Experimental intrauterine growth retardation in the sheep, Am. J. Obstet. Gynecol. 112:566, 1972.
- 14. Barcroft, J., and Barron, D. H.: Observations of the form and relations of the maternal and fetal vessels in the placenta of the sheep, Anat. Rec. 94:569, 1946.
- 15. Levin, D. L., Hyman, A. I., Heymann, M. A., and Rudolph, A. M.: Fetal hypertension and the development of increased pulmonary vascular smooth muscle: A possible mechanism for persistent pulmonary hypertension of the newborn infant, J. Pediatr. 92:625, 1978.

# Characterization of triacylglycerol lipase activity in human amniotic fluid

CHARLES MERGER
ANNE VALETTE
HENRI RUF
JEAN BOYER
Marseille, France

A radiochemical assay was used to measure the triacylglycerol lipase activity found in normal human amniotic fluid at term. Enzyme activity was characterized in a partially purified extract of amniotic fluid and was found to be optimal at pH 8 0  $\pm$  0.2 in the presence of 5 mM sodium taurocholate, with the use of emulsified tri-[³H]oleo•i glycerol as the substrate. The assay described made it possible to determine the lipase activity in as little as 25  $\mu$ l of a 12,000  $\times$  g supernatant of whole amniotic fluid as the source of enzyme. The ipase appeared to be distinct from another triacylglycerol lipase measurable in fetal membranes. In turn, it was shown that the amniotic fluid enzyme exhibited several catalytic properties which resembled those of pancreatic lipase. i.e., its substrate specificity, the bimodal effect of bile salt, and the influence of authentic pancreatic colipase on the catalytic process. The results suggest that the assay of triacylglycerol lipase activity may be clinically useful in the detection of enzyme abnormalities in human amniotic fluid. (Am. J. Obstet. Gynecol. 138:68, 1980.)

BIOCHEMICAL determinations in amniotic fluid (AF) have been used increasingly in the prenatal diagnosis of a number of disorders. Recently, Mohide and Hill-suggested that the presence of high levels of lipase activity in human AF might be regarded as an indication of potential problems, such as gastrointestinal obstruction. Although this constitutes an interesting observation, the fact that there is at present no information on the nature, biochemical behavior, and activity levels of a triacylglycerol lipase in AF under normal conditions points to the need for a better knowledge of the enzyme.

Lipases (EC 3.1.1.3) are carboxy ester hydrolases which act on water-insoluble esters of glycerol by heterogeneous catalysis,<sup>2</sup> where the enzyme adsorbs to the interface of the aggregated substrate and water.

From the Service d'Explorations Métaboliques and the Maternité de la Belle-de-Mai, Centre Hospitalier Régional de Marseille.

Sponsored by the Fondation pour la Recherche Médicale Française.

Received for publication February 19, 1980. Accepted March 28, 1980.

Reprint requests: Dr. J. Boyer, Service d'Explorations Métaboliques, Hôpital de la Conception, 13385 Marseille, Cédex 4, France. Lipases have been studied in numerous tissues and biologic fluids and are classified according to both the tissue in which they are found and the main type of fatty ester that they hydrolyze. The present study is concerned with the characterization of a triacylglycerol lipase in AF obtained from the pregnancies of normal women before spontaneous vaginal delivery. We describe the optimal conditions of the catalytic process in an assay system whose sensitivity and specificity have been ascertained by the use of a radiolabeled triacylglycerol as the substrate. In turn, we examine the usefulness of this technique as a possible clinical assay for the enzyme.

### Material and methods

Tri-[9,10-3H] oleoyl glycerol (344 Ci/mole) and [9,10-3H] oleic acid (50 Ci/mmole) were purchased from the Radiochemical Centre, Amersham, England, and CEA, France, respectively. [9,10-3H] Oleoyl glycerol and unlabeled dioleoyl glycerol were synthesized in the laboratory by conventional methods. Unlabeled trioleoyl glycerol and dioleoyl glycerol (about 40% 1,2-dioleoyl glycerol and 60% 1,3-dioleoyl glycerol) (Sigma Chemical Co., St. Louis, Missouri) were obtained over 98% pure by chromatography on Florisil.3 Ammonium sulfate (Prolabo, France) was re-

X

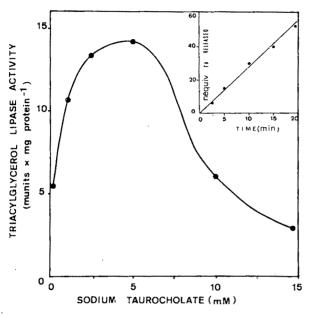


Fig. 1. Triacylglycerol lipase activity of human AF as a function of increasing concentration in sodium taurocholate. Enzyme assays were carried out at 37° C for 15 minutes at pH 8 with an AS-75 extract of AF (0.25 mg of protein), and with 1 mM tri-[3H]oleoyl glycerol used as the substrate. Inset: Time course of the lipolytic process run as above in the presence of 5 mM sodium taurocholate. FA, Fatty acid.

crystallized from ethylenediaminetetra-acetic acid.4 Sodium taurocholate was from Nutritional Biochemical Corporation., Cleveland, Ohio. Fatty acid-poor bovine serum albumin was from Calbiochem-Behring Corporation, La Jolla, California. Purified porcine colipase was donated by C. Chapus (Centre de Biologie Moléculaire, C.N.R.S., Marseille). All other reagents were of the highest purity commercially available.

Preparation of samples of AF. Samples of AF were obtained during spontaneous labor from normal women after at least 38 weeks of gestation. Amniocentesis was performed by puncture of the membranes through an amnioscope at the time of rupture of the membranes before vaginal delivery. The fluids which were highly pigmented or which contained blood or meconium were discarded. Samples were kept at 4° C and processed within 2 to 6 hours after collection.

The kinetic properties of the enzyme in AF were investigated by using partially purified AF samples as the source of enzyme. In pilot studies, it had been shown that, when samples of whole AF were subjected to sequential centrifugation at 600 × g for 10 minutes,  $12,000 \times g$  for 20 minutes, and  $105,000 \times g$  for 2 hours, over 80% of the total amount of activity in whole AF was recovered in the 105,000 × g supernatant, thus indicating that the lipase was essentially water-soluble.

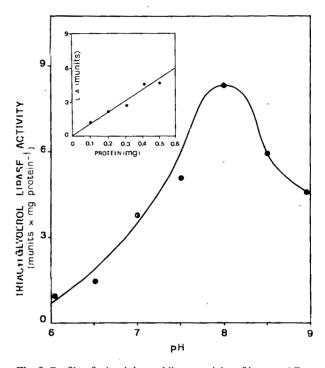


Fig. 2. Profile of triacylglycerol lipase activity of human AF as a function of pH. Enzyme assays were carried out at 37° C for 15 minutes with an AS-75 extract of AF (0.45 mg of protein) in 0.1M Tris-HCl with 1 mM tri-[3H] oleoylglycerol used as the substrate, in the presence of 5 mM sodium taurocholate. Inset: Effect of enzyme concentration on lipase activity (LA); conditions as above, at pH 8. Four assays contributed to each point.

Therefore, for the analytical studies, the AF samples were first centrifuged at 12,000 × g for 20 minutes in order to remove contaminating cells and debris, as well as floating material. Then the proteins were precipitated by adding solid crystallized ammonium sulfate to the supernatant up to 0.75 of saturation. During precipitation, the pH was maintained around 7.4 by the addition of dilute NH<sub>4</sub>OH. The precipitate was permitted to accumulate for 4 to 6 hours at 4° C, centrifuged for 30 minutes at 12,000  $\times$  g, and reconstituted to 2 to 5 ml of 50 mM sodium phosphate buffer (pH 7.4), thus affording approximately a tenfold concentration over the original. The resulting preparation was dialyzed for 24 hours against three 500 ml changes of the same buffer, and the dialysate, referred to as "AS-75," was used as the source of enzyme. This preparation could be stored frozen for about 2 months, but each freezing-thawing process decreased by approximately 20% its content of lipase activity.

Preparation of extracts from fetal membranes. Fetal membranes (chorioamnion) were removed immediately post partum and rinsed in cold saline solution in order to remove contaminating blood and AF cells.

**Table I.** Reversion of the inhibitory effect of sodium taurocholate on the AF lipase activity by increasing concentrations of colipase

Sodium taurocholate (mM)	Colipase (µg)	Triacylglycerol lipase activity (mU/mg protein,
	_	6.2
5	_	13
10	-	7.0
15	•	4.1 ·
15 `	7.5	8.8
15	15	11
15	30	16
15	75	13

Assays were carried out at 37° C for 15 minutes at pH 8 with an AS-75-extract as the source of enzyme. The indicated amounts of taurocholate and colipase were added to the incubation medium without additional sonication. The values are those of a representative experiment.

**Table II.** Lipase activity in human AF and fetal membranes: Comparative values with triester, diester, and monoester as substrates

	Lipase activity (mU/mg protein)				
Substrates	AF	Amnion	Chorion		
Triester	23	2.3	2.4		
Diester	5.7	4.2	3.5		
Monoester	n.d.	1.5	1.7		

Assays were carried out as indicated in the *Material and Methods* section. The AF preparation was an AS-75 extract. n.d. = Not detectable.

The amnion and chorion laeve were dissected, and specimens of each tissue were washed with cold 0.25M sucrose, blotted, and weighed. Aliquot fractions of each tissue were homogenized in 0.25M sucrose (3 ml/gm tissue) with the use of an Ultra-Turrax homogenizer (1 minute, top speed, 2 to 6° C). The homogenates were centrifuged at  $750 \times g$  for 10 minutes, and the resulting supernatant was used for the assay of lipase activities.

Enzymatic assays. Triester, diester, and monoester lipase activities were assayed with the use, respectively, of tri- $[9,10^{-3}H]$  oleoyl glycerol,  $di-[9,10^{-3}H]$  oleoyl glycerol, and  $[9,10^{-3}H]$  oleoyl ethanol as substrates. Since oleoyl ethanol and monooleoyl glycerol are most probably hydrolyzed in mammalian tissues by the same enzyme, there are technical advantages in using oleoyl ethanol as the substrate for the assay of monoester lipase. All radiolabeled substrates were introduced in the assay medium as a sonic emulsion (Branson sonifier model B-12, microtip at setting 4 for 1 minute, at 4° C) made in an aqueous solution of albumin (0.5%, w/v).

Unless otherwise stated, the assay for triester lipase

activity contained 0.1M Tris-HCl, 0.5% (w/v) albumin, 5 mM sodium taurocholate, 1 mM emulsified tri-[ $^3$ H] oleoyl glycerol (about  $10^6$  cpm), and the enzyme (usually 0.01 to 0.05 ml of partially purified extract) in a final volume of 1 ml at 37° C at the pH optimum of  $8.0 \pm 0.1$ . Diester lipase activity was assayed with 1 mM di-[ $^3$ H] oleoyl glycerol as the substrate in a reaction system otherwise identical to that used for triester lipase. Monoester lipase activity was assayed with 1 mM [ $^3$ H]oleoyl ethanol, as previously described. $^5$ 

In all cases, assays were carried out in duplicate in a shaking water-bath (120 cycles/min). The release of [³H] oleic acid was linear during the 15-minute period of assay and served to monitor the rate of the lipolytic process. Extraction, purification, and counting of the radiolabeled acid were carried out as previously reported. Duplicate assays were reproducible within 10% of [³H] oleic acid released. The lower limit of assay sensitivity was 0.05 mU of lipase activity. One milliunit of activity corresponded to the release of 1 nmole of acid per minute. H radioactivity was measured in an Intertechnique liquid-scintillation spectrometer, type SL 4020, with a counting efficiency of 64%.

Protein content was determined by the method of Lowry, with bovine serum albumin used as the standard.

### Results

Fig. 1. shows that the measured AF triacylglycerol lipase activity varied with the concentration of bile salt in the assay medium. The rate of hydrolysis was increased 3.5 times when the concentration of taurocholate was raised from 0 to 5 mM. At higher concentrations of taurocholate, the rate of hydrolysis decreased markedly and the bile salt became inhibitory. Comparable effects were observed with deoxycholate and glycocholate, although the degree of stimulation was of lesser amplitude. Activity rates were unchanged in the presence of 5 mM CaCl<sub>2</sub>, whether a bile salt was or was not present in the assay medium.

The effect of the pH of the bulk phase on the lipase activity is presented in Fig. 2. Maximal rates of hydrolysis were measured at pH  $8.0 \pm 0.2$ . At this pH value, and in the presence of 5 mM taurocholate, the purified enzyme hydrolyzed trioleoyl glycerol at an activity rate nearly constant during 20 minutes (Fig. 1, inset). The dose-response curve was linear with the amounts of protein added as the enzyme source up to at least 0.5 mg (Fig. 2, inset). Therefore, amounts of protein in the range of 0.05 to 0.5 mg were used in each incubation medium.

Studies with pancreatic lipase have shown that a pancreatic protein, designated as colipase, has the specific ability to reverse the inhibitory effect of high concen-

trations of bile salts on the pancreatic enzyme.<sup>7</sup> Table I shows that the effect of colipase on the AF enzyme resembled its effect on the pancreatic lipase: the addition to the lipolytic medium of increasing amounts of a purified preparation of porcine colipase completely reversed the inhibitory effect of 15 mM taurocholate on the lipolytic process.

The origin(s) of the lipase activity in AF from the pregnancies of normal women is(are) unknown. Comparative experiments with different substrates (Table II) suggested that the AF enzyme has a profile different from that of the lipase assayed in human fetal membrane extracts. The ratio of triester to diester lipase activity averaged 4 for the AF enzyme, as compared to about 0.6 for the enzyme in the membrane extracts. Moreover, it was shown that, although the membrane extracts contained measurable levels of monoester lipase activity, no such activity could be detected in the AF preparations. Taken together, these findings are consistent with the view that both fetal membranes contain the same lipase and that this lipase exhibits catalytic properties different from those found for the AF enzyme.

In practice, the direct assay of triacylglycerol lipase in AF requires caution. As shown earlier for other lipolytic systems, 6 AF compounds added with the enzyme to the assay medium may interact with the substrate interface and modify in an unpredictable manner the measured reaction rates. This especially holds for samples of whole AF, 600 × g or 12,000 × g supernatants used as sources of enzyme. Whereas the use of 1 mM tri-[3H]oleoyl glycerol as substrate gave optimal enzyme kinetics with an AS-75 extract (Figs. 1 and 2), an incorrect dose-response curve was obtained with a 12,000 × g supernatant (Fig. 3) because of nonlinear reaction rates. Fig. 3 shows that the same assays carried out with 2 mM tri-[ $^3$ H]oleoyl glycerol (about 1.5  $\times$  10 $^6$ cpm) gave a straight-line relationship for protein concentrations up to 0.5 mg. Under these conditions, assays were linear for at least 30 minutes, and it was possible to determine triacylglycerol lipase activity in as little as 25  $\mu$ l of an AF-12,000 × g supernatant.

### Comment

This study describes some of the properties of the triacylglycerol lipase in human AF at term. When this lipase activity was assayed under optimal conditions with radiolabeled trioleoyl glycerol as the substrate, the activity levels averaged 10 mU/ml (range, 5.1 to 16.4 mU for eight experiments) of original fluid. This range of activity is far below that found, for instance, in human milk, which contains about 103 mU of lipase activity per milliliter.8 The normal human duodenal

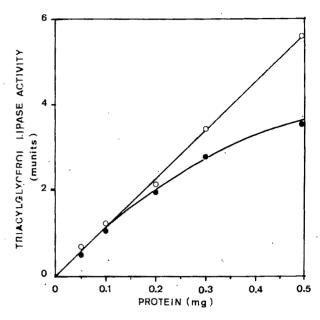


Fig. 3. Triacylglycerol lipase activity of human AF as a function of the amount of enzyme at two concentrations of tri-[3H]oleoylglycerol: 1 mM (•••) and 2 mM (o-o). Assays were carried out with a 12,000 × g supernatant of whole AF as the source of enzyme. The incubation medium was otherwise identical to that described in the Material and methods section.

juice contains still higher levels (usually above 8.105 mU/ml). By contrast, extracts from several human tissues contain, on a volume basis, amounts of lipase (viz, 5 to 20 mU/ml of crude adipose tissue extract) comparable to those found in AF.

Mohide and Hill1 report that freshly analyzed samples of whole AF obtained in unrelated conditions had a mean lipase activity of 62.1 mU/ml.\* The apparent difference by a factor of 6 between these results and ours may have at least two possible causes. The assay system used by Mohide and Hill was a titrimetric technique made optimal by Tietz and Repique9 for the routine determination of lipase activity in human serum. In this technique, the continuous titration of small amounts of fatty acids with highly diluted alkali (10 mM) may expose the lipolytic rates to an overestimation, because of the uptake and titration of acidic substances from the air. The relatively high mean level reported by Mohide and Hill may also derive from the variety of clinical conditions that contribute to the calculation of the mean value, some of these conditions possibly being associated with increased levels of AF lipase activity.

It was not within the scope of this work to define the source(s) of triacylglycerol lipase activity in human AF.

\*In this report,1 "mmoles per liter" should read "units per liter," as defined by Tietz and Repique<sup>9</sup> (Hill, R. E.: Personal communication).

However, as stated above, on the basis of substrate specificity studies, this lipase seems to be different from a triacylglycerol lipase measurable in fetal membrane extracts (Table II). Likewise, the AF enzyme appears to be distinct from a phospholipase also present in the fetal membranes, the activity of which is increased in the presence of calcium. 10 In many respects, the AF enzyme exhibited catalytic properties similar to those of pancreatic lipase: (1) Its maximal activity occurred in the alkaline pH range. (2) Triacylglycerol was a preferential substrate, and diester and monoesters were hydrolyzed at much slower rates. (3) Sodium taurocholate had, at low concentrations, a stimulatory effect on the reaction process, and, at higher concentration, an inhibitory effect. (4) The latter effect was fully reversed

by the addition of authentic pancreatic colipase to the lipolytic medium. To date, we have not been able to ascertain whether the AF enzyme simply derives from the fetal or maternal pancreatic lipase or constitutes a distinct entity sharing only similarities with these enzymes.

Further work is needed to determine the content of triacylglycerol lipase activity in AF at various gestational ages. Knowledge of eventual variations in activity levels constitutes a prerequisite for the reliable detection of enzyme abnormalities. This is especially mandatory for the interpretation of low levels of AF lipase, as might be the case in enzyme defects, such as congenital pancreatic lipase deficiency.11

### REFERENCES

- 1. Mohide, P. T., and Hill, R. E.: Amniotic fluid lipase in two cases of duodenal obstruction, Am. J. OBSTET. GYNECOL.
- 2. Desnuelle, P.: The lipases, Enzymes 7:575, 1972.
- 3. Carroll, K. K.: Separation of lipid classes by chromatography on Florisil, J. Lipid Res. 2:135, 1961.
- 4. Beizenherz, G., Boltze, H. J., Bucher, T., Czok, R., Garbade, K. H., Meyer-Arendt, E., and Pfleiderer, G.: Diphosphofructose aldolase, phosphoglyceraldehyde dehydrogenase, lactic acid dehydrogenase, glycerophosphate dehydrogenase and pyruvate kinase from muscle, Z. Naturforsch. (C) 8:555, 1953.
- 5. Arnaud, J., and Boyer, J.: Lipolytic activity of whole isolated liver cells in aqueous suspension, Biochim. Biophys. Acta 424:460, 1976
- Giudicelli, H., Pastré, N., and Boyer, J.: Lipolytic activity of adipose tissue, Biochim. Biophys. Acta 348:221, 1974.

- 7. Borgström, B., Erlanson-Albertson, C., and Wieloch, T.: Pancreatic colipase: Chemistry and physiology, J. Lipid Res. 20:805, 1979.
- 8. Jubelin, J., and Boyer, J.: The lipolytic activity of human
- milk, Eur. J. Clin. Invest. 2:417, 1972. Tietz, N. W., and Repique, E. V.: Proposed standard method for measuring lipase activity in serum by a continuous sampling technique, Clin. Chem. 19:1268, 1973.
- 10. Okazaki, T., Okita, J. R., McDonald, P. C., and Johnston, J. M.: Initiation of human parturition. X. Substrate specificity of phospholipase A2 in human fetal membranes, Am. J. Obstet. Gynecol. 130:432, 1978.
- 11. Figarella, C., Negri, G. A., and Sarles, H.: Presence of colipase in a congenital pancreatic lipase deficiency, Biochim. Biophys. Acta 280:205, 1972.

## GYNECOLOGIC URODYNAMICS

Endoscopic Light/CO<sub>2</sub> source interfaces with Life-Tech's urodynamic instrumentation allowing assembly of systems ranging in complexity from a simple, compact urethral profilometry/cystometry/urethroscopy instrument to a complete multi-channel urodynamics laboratory. A unique aspect of all Life-Tech's urodynamic systems is their modularity. Initially a minimal system exactly

tailored to the user's needs can be acquired. At any later time, the system can be expanded and updated as needs change or new knowledge becomes available.

Life-Tech is the oldest and largest manufacturer of urodynamic equipment. Our instrumentation is Underwriters Laboratories listed. It is also the finest, most accurate and easiest-to-use diagnostic urodynamics test equipment

available. Service support for Life-Tech's products is provided by over 65 regional service centers backed by a fully equipped and staffed factory service facility. Trained, experienced Life-Tech personnel install all systems and provide in-service instruction on instrument operation.

For additional information or for a demonstration in your office or clinic, please write or phone.



|Cooler and quieter than comparable | endoscopic light sources

Unsurpassed brightness

Dual lamps for safety backup

Couplers to fit any endoscopic fiber-optic light cable

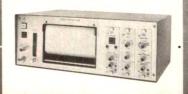
Interfaces with a wide selection of Life-Tech urodynamic instrumentation











### OB/GYN PHYSICIAN

OB/GYN Physician to join Health Care Plan. Opportunity for Board certified or qualified physician in innovative staff model HMO. Negotiable salary, outstanding fringe benefits, nurse-midwife, certified family practitioners, university affiliated, chance to build your own department. Position available anytime in 1980.

C.V. to Medical Director, Health Care Plan Medical Center, 120 Gardenville Parkway West, West Seneca, N.Y. 14224 or call 716-668-3600.

### DELIVERY SUITE PHYSICIAN

Department of Obstetrics & Gynecology, E. A. Conway Memorial Hospital in Monroe, Louisiana. Full-time physician needed for delivery room coverage. Salary negotiable with education and experience.

Send resume to:
Dr. Dale R. Dunnihoo
Professor and Director
of Obstetrics & Gynecology
E. A. Conway Memorial Hospital
P. O. Box 1881
Monroe, Louisiana 71201
AN EQUAL OPPORTUNITY EMPLOYER

### OB/GYN

Prepaid medical group practice. established 1976. Two suburban care centers, each with 3 or 4 BC/BE OBG's. New comprehensive facilities. Well-staffed for clinical support, including Nurse Practitioners and hospital residents. Attractive salary structure and liberal fringes. Starting salary based on experience. Recruitment and relocation expenses covered. Unusually livable city. Send CV or call: Michael R. Soper, M.D. Medical Director 6801 E. 117th Street Kansas City, Missouri 64134.

# OBSTETRICIAN/ GYNECOLOGIST

Board certified/eligible Ob-Gyn wanted for group in lovely S.E. Mass. community. One office-one hospital. Unique coverage schedule with a second group currently allows every eighth night call. No pregnancy terminations. Great opportunity.

Contact:
T. P. McCORMACK, M.D.
60 Brigham St.
New Bedford, Ma., 02740.
Phone: 617-997-2200

# Choose a practice you can live with.

Hospital Corporation of America knows of many practice opportunities in communities across the nation where we can match a physician's professional needs and personal desires with an attractive community that needs his or her skill.

HCA owns and manages more than 150 hospitals from coast to coast in settings ranging from small, rural towns to large metropolitan centers. Practice opportunities are available in solo, groups, associations, and partnerships.

And HCA will help ease the way when you and your practice relocate. Upon

arrival, you should find a solid practice, conveniently located offices, and the medical support and modern equipment you need.

Contact HCA today. Let our free, no obligation Professional Relations Program match your needs with an HCA practice opportunity. Just send your curriculum vitae, along with information on your personal, professional, and geographical interests to:

Charles M. Wooden, Director, Professional Relations, Hospital Corporation of America, One Park Plaza, Nashville, TN 37203. Telephone toll free 1-800-251-2561 or call collect (615) 327-9551.

### Hospital Corporation of America.

#### Annual Microscopic and Clinical Review In Ob-Gyn Pathology and Oncology

Raymond H. Kaufman, M.D. Byron J. Masterson, M.D. Ralph M. Richart, M.D. Daniel K. Roberts, M.D., Ph.D. Shelby Rose, M.D.

Felix Rutledge, M.D.
Joe Leigh Simpson, M.D.
J. Taylor Wharton, M.D.
J. Donald Woodruff, M.D.
Ralph M. Wynn, M.D.

When: December 7-11, 1980

Where: Wichita Hilton Inn, Wichita, Kansas

Course Description: 5 day in-depth review of the reproductive system; daily didactic sessions with kodachrome slides from 8:00-3:00; microscopic lab 3:30-5:30; and individual case consultations.

Designed For: Practitioners and residents in Obstetrics & Gynecology desiring a review of pathology and oncology of the female genital tract.

Registration: Limited; must be received by November 24,

CME Credit: As an organization accredited for continuing medical education, The University of Kansas School of Medicine-Wichita, designates that this continuing medical education activity meets the criteria for 35 credit hours in Category I of the Physician's Recognition Award of the American dedical Association. This course has been approved for 35 cognates, Formal Learning, by the American College of Obstetricians and Gynecologists.

Tuition: \$600 includes didactic sessions, microscopic lab, current syllabus, selected 35mm slides and microscopic slides. A microscope will be required with a limited number available for rent locally.

For Further Details and Registration Contact: Karen Call, Division of Postgraduate Education, The University of Kansas School of Medicine-Wichita, 1001 N. Minneapolis, Wichita, . Kansas 67214 or (316) 268-8261.

# FACULTY POSITIONS OBSTETRICS AND GYNECOLOGY UNIVERSITY OF TENNESSEE

#### Clinical Education Center Chattanooga

Positions available in Perinatology and Ambulatory Care in the Department of Obstetrics and Gynecology at the Clinical Education Center at Chattanooga. Obstetrics and Gynecology Residency Program in a University Affiliated Hospital. Approved program with ten residents. Rotation of Medical Students for Core Clerkships and Electives. Faculty appointment. Must be Board Certified Obstetrics and Gynecology. Please direct inquiries and C. V. to:

Norman L. Stahl, M.D. Chairman, Department of Obstetrics and Gynecology Suite 400-921 East Third Street Chattanooga, Tennessee 37403 Phone (615) 756-4856

The University of Tennessee is an Affirmative Action and Equal Employment Opportunity Employer



INDICATIONS: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective for the relief of moderate to moderately severe pain in those situations where the physician wishes to add a mild sedative effect. Final classification of the less-than-effective indications requires further investigation.

NTRAINDICATIONS: Hypersensitivity to dihyocodeine, promethazine, aspirin, phenacetin. IRNINGS: Salicylates should be used with treme caution in the presence of peptic er or coagulation abnormalities.

ug Dependence: Dihydrocodeine can proce drug dependence of the codeine type d therefore has the potential of being used. Psychic dependence, physical depennce and tolerance may develop upon eated administration of dihydrocodeine.

and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, dihydrocodeine is subject to the provisions of the Federal Controlled Substances Act. Usage in Ambulatory Patients: Dihydrocodeine and promethazine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Synalgos-DC should be cautioned accordingly. Interactions with other Central Nervous System Depressants: Patients receiving other narcotic analgesics, general anesthetics, other phenothiazines, tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Synalgos-DC may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Patients who have demonstrated a hypersen-

sitivity reaction (e.g. blood dyscrasia, jaundice) with a phenothiazine should not be reexposed to any phenothiazine, including Synalgos-DC, unless in the judgment of the physician the potential benefits of the treatment outweigh the possible hazards. **Usage in Pregnancy:** Reproduction studies have not been performed in animals. There is no adequate information on whether this drug may affect fertility in human males and females or has a teratogenic potential or other adverse effect on the fetus. **Usage in Children:** Since there is no experience in children who have received this drug, safety and efficacy in children have not been established.

PRECAUTIONS: Phenacetin has been reported to damage kidneys when taken in large amounts for a long time. Promethazine should be administered cautiously to patients with cardiovascular or liver disease. Synalgos-DC should be given with caution to certain patients such as the elderly or debilitated, and those with hypothyroidism, Addison's disease and

prostatic hypertrophy and urethral stricture.

ADVERSE REACTIONS: The most frequently observed reactions include lightheadedness, dizziness, drowsiness, sedation, nausea, vomiting, constipation, pruritus, skin reactions, and

rarely, hypotension

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. Synalgos-DC is given orally. The usual adult dose is 2 capsules every 4 hours as needed for pain DRUG INTERACTIONS: The CNS depressant effects of Synalgos-DC may be additive with that of other CNS depressants. See Warnings. Aspirin may enhance the effects of anticoagulants and inhibit the uricosuric effects of uricosuric agents.

Consult direction circular before prescribing.

### IVES LABORATORIES INC.

New York, NY 10017 Dedicated to improving the quality of life, through Medicine®



#### GYNECOLOGY

### Late recurrences of gestational trophoblastic neoplasia

THOMAS C. VAUGHN, M.D. EARL A. SURWIT, M.D. CHARLES B. HAMMOND, M.D.

Durham, North Carolina

Presented are two cases of recurrence of gestational trophcolastic neoplasia more than 1 year after apparently successful therapy. Both patients initially had had nonmetastatic disease, were clinically free of disease, and had had repetitively negative serum radioimmunoassay titers for the beta subunit of human chorionic gonadotropin for 2 to 3 years. The development of these late recurrences re-emphasizes the need for prolonged follow-up monitoring of patients after apparently successful therapy for gestational trophoblastic neoplasia. AM. J. OBSTET. GYNECOL. 138:73, 1980.)

GESTATIONAL trophoblastic neoplasms are malignant tumors that arise from the trophoblast of human pregnancy and are invariably associated with the secretion of human chorionic gonadotropin (hCG), which is usually produced in proportion to the number of viable tumor cells present.1 Although this tumor can be one of the most rapidly progressive and fatal neoplasms in women, it has become, over the last 25 years, since the introduction of systemic chemotherapy,2 one of the most curable. Such an evolution in response is primarily due to the availability of effective chemotherapeutic agents and the usefulness of monitoring by sensitive assays for hCG. In addition, the identification of high-risk factors and subsequent categorization of patients with metastatic disease into different groups<sup>3</sup> have allowed more aggressive therapy as the initial approach for patients with increased risk. This grouping

> From the Southeastern Regional Center for Trophoblastic Disease, Department of Obstetrics and Graecology, Duke University Medical Center.

Received for publication January 23, 1980.

Revised March 12, 1980.

Accepted March 14, 1980.

Reprint requests: Charles B. Hammond, M.D., Box 3143-OG, Duke University Medical Center, Durham, North Carolina 27710.

has further allowed substantial reduction in toxicity for the patients in the categories of better prognosis without jeopardizing the cure rates.

Patients with malignant trophoblastic neoplasia have an excellent prognosis; in fact, Hammond and associates³ have reported a remission rate approaching 100% in a large group of patients with nonmetastatic and "good" prognosis metastatic disease. After a close follow-up of 1 year and repetitively negative sensitive assays for hCG (<5 mIU/ml by beta-subunit radioimmunoassay for hCG), the patient is considered to be cured, and, if she desires, she may resume childbearing. The recurrence of gestational trophoblastic neoplasia (GTN) after 1 year of documented remission has been exceedingly rare.

This report presents the cases of two patients who developed recurrence of GTN after being clinically free of disease for longer than 1 year.

#### Case reports

Patient 1. D. W., a 32-year-old white woman, para 9-1-8, was referred to this Center in July, 1975, for evaluation of suspected choriocarcinoma.

After normal menarche and unremarkable menstrual function, the patient had experienced eight pregnancies productive of normal infants. In February, 1975, the patient became pregnant (last normal menstrual period in November, 1974), but vaginal bleeding was noticed. Angiography was performed because of clinical suspicion, and an hydatidiform mole was diagnosed. Subsequently, the patient underwent hysterotomy evacuation of a molar gestation, with bilateral ligation of the fallopian tubes and an appendectomy. She was followed, and in May, 1975, because of heavy bleeding, underwent a curettage which yielded residual molar tissue. A urinary hCG value was reported as >1,500, <7,500. The patient was then referred to this institution.

Metastatic workup (brain scan, liver scan, chest x-ray film) done on admission in July, 1975, was negative. The serum beta-hCG was 59.3 mIU/ml. Methotrexate. 20 mg intramuscularly, was administered daily for 5 days per treatment course, and after two such courses the beta-hCG titer was negative; she then received one additional course. Subsequently, the patient was followed with monthly determination of hCG titers for 3 months, then every other month for 6 months, and then every third month, and all were negative. The patient began Norinyl 1 + 80 during hospitalization but discontinued the drug 3 months later. Menses resumed in cyclic fashion until she missed a period in July, 1978. She experienced some heavy vaginal bleeding in August, and was seen by her local physician at that time, when a serum beta-hCG returned to 117 mIU/ml.

Subsequently, the patient was readmitted to this institution in September, 1978 (3 years after original chemotherapy), for further evaluation. The findings of the physical examination were completely within normal limits, including those of the pelvic examination. Endometrial biopsy failed to reveal any pathologic condition. Metastatic work-up was again normal. Abdominal arteriography by percutaneous right femoral catheterization demonstrated a questionable "tumor blush" in the uterus. Because of the likelihood of recurrent disease in the pelvis, the patient underwent exploratory laparotomy on the third day of actinomycin D therapy (11 mcg/kg intravenously daily for 5 days). Exploration of the abdomen and pelvis was negative, and total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. Choriocarcinoma was found in one area of the uterus. Midsegments of the fallopian tubes were surgically absent, and histologic examination confirmed obliteration of the tubal lumen. After hysterectomy and the first course of chemotherapy, the serum beta-hCG declined to 5.2 mIU/ml; it became negative (< 5 mIU/ml) during the second course of chemotherapy. The patient

subsequently left the hospital against medical advice, after the second course of actinomycin D. Fortunately, repetitive follow-up titers and examinations have remained negative.

**Patient 2.** J. S., a 28-year-old white woman, para 2-1-1, was referred to this Center in 1976, for treatment of trophoblastic malignancy.

After normal menarche and unremarkable menstrual function, the patient had been delivered of a live term infant in 1971. In 1976, a hydatidiform mole was evacuated by curettage; postevacuation hCG titers remained elevated and then plateaued and rose to 425,000 IU/L. Subsequently, the patient was referred to this institution, where, after a negative metastatic survey, she was treated with methotrexate (20 mg intramuscularly daily for 5 days). The serum beta-hCG was undetectable after eight courses of methotrexate, and the patient received one additional course of chemotherapy.

Ovral, which had been used for contraception afterevacuation of the hydatidiform mole, was continued, and the patient did well until October, 1978, when she presented to her local physician with amenorrhea and symptoms suggesting pregnancy. A serum beta-hCG titer that had been 15.6 mIU/ml the previous month was 25.6 mIU/ml 4 weeks later. The patient developed suprapubic cramping and vaginal bleeding. She was readmitted to this hospital and underwent curettage of the uterus and diagnostic laparoscopy to exclude ectopic pregnancy. The endometrial tissue demonstrated "changes consistent with progestin administration," but no evidence of any trophoblastic tissue was seen nor were any abnormalities found at laparoscopy. Serum beta-hCG at this time was 56.5 mIU/ml. While still continuing to use oral contraceptives, the patient was subsequently referred for further evaluation. On readmission here, the findings of physical examination were normal and metastatic survey was negative. Repeat curettage showed proliferative endometrium. The patient was begun on the 9-day Bagshawe4 multiagent chemotherapy regimen and received four total courses of the medication. Two of the courses were given after the beta-hCG determination was negative.

The patient did well until February, 1959 (2 months later), when the beta-hCG level again rose to 93.7 mIU/ml. Metastatic work-up was again negative, and the patient underwent total abdominal hysterectomy. An 8 mm focus of choriocarcinoma was found in the uterus. The patient was not given any chemotherapy. Subsequently, the beta-hCG determinations were repetitively negative and the findings of the examinations were normal.

 $\lambda$ 

#### Comment

Nonmetastatic GTN is defined as disease confined to the uterus without evidence of distant metastases. Approximately 75% of patients will develop this disease after molar pregnancy; the remainder of the cases will follow other types of pregnancies.<sup>5</sup> In either situation the diagnosis is established by curettage or hysterectomy and the determination of a plateauing or rising hCG titer. Metastatic staging is performed to exclude involvement of other likely organs. Patients with GTN in whom disease is found outside the uterus have metastatic disease and are classified as having "good" or "poor" prognosis. This categorization was derived from data which demonstrated that the success of chemotherapy was influenced by the nature of the antecedent pregnancy, the duration of disease, the height of the initial pretreatment hCG titer, previous chemotherapy, and the presence or absence of either cerebral or hepatic metastases.3

Regardless of the classification of the patient or the type of therapy used, monitoring of therapy is primarily done through repetitive sensitive gonadocropin titers, and the treatment of malignant trophoblastic disease is continued until the hCG titer has retuned to normal by a precise and sensitive assay. Suppression of pituitary gonadotropin via oral contraceptives in all patients who do not have any contraindications to these agents has been used to allow a more accurate determination of remission, since many hCG assays also react with pituitary luteinizing hormone.3 The use of the radioimmunoassay for the serum beta subunit of hCG is currently the most specific and reliable technique for sensitive monitoring of hCG.6

The diagnosis of remission from trophoblastic disease is not made until there are three consecutive weekly negative gonadotropin titers. Both cf these patients clearly demonstrated consecutively negative sensitive hCG titers (radioimmunoassay for serum betahCG) and were considered to be in remission until elevation of the titers recurred.

GTN is characteristically a rapidly progressive disease which usually does not remain quiescent for a long period of time. An unexpected intervening pregnancy during the time of suspected remission is unlikely for either of these two patients, since D. W. had had a tubal ligation (confirmed by pathologic specimen) and J. S. had used oral contraceptives since her initial diagnosis. Thus, it appears that the years of remission actually represent persistence of disease in a qu escent state, although the mechanism for this dormant state is unclear.

It appears that the uterus may be a privileged site for recurrence of nonmetastatic GTN. Both patients were found to have residual foci in the uterus; in fact, all of the patients at this Center who had recurrence of nonmetastatic GTN experienced the recurrence in the uterus.8 This further supports the use of hysterectomy as an important aspect of therapy for patients with nonmetastatic GTN who do not desire further childbearing. Hysterectomy coincident with the institution of systemic chemotherapy has been shown to sign ficantly reduce the duration of hospitalization and the amount of chemotherapy used to achieve remission.9

The method of evacuation of the hydatidiform mole in D. W. may have contributed to increasing the potental for malignant sequelae and later recurrence. Data row suggest that this method of evacuation of molar Essue may influence the incidence of postevacuation mailgnancy (curettage, 19%; hysterotomy, 36%), but these data are trends only 10 and do not necessarily show an increase in the incidence of recurrence once a remission has been achieved. Even if there is no increase n malignancy or its recurrence, hysterotomy is still associated with a greater loss blood and greater postoperative morbidity; and if further childbearing occurs, resarean section will usually be required. Thus, hysterotomy is not currently recommended as a method for evacuation of molar pregnancy. Primary evacuation by suction curettage is preferable if further childbearing is desired.5

It is important to note that one of the two patients (J.S.) with nonmetastatic GTN had an initial hCG level markedly elevated to 425,000 IU/L. This level is unusual in patients with nonmetastatic GTN and may have contributed to recurrence, since it implies an increased volume of tumor, which usually requires more chemotherapy, and perhaps has a greater potential for developing drug resistance.

Late recurrences of GTN are very rare; the incidence is less than 1% (Over 257 patients with GTN have been treated at this Center.) However, the fact that it has recurred in these patients reemphasizes the need for prolonged follow-up of patients with GTN.

#### REFERENCES ,

- 1. Hammond, C. B., Schmidt, H. J., and Parker, R. T.: Gestation trophoblastic disease, in Gynecologic Oncology, McGowan, p. 287.
- 2: Li, M. D., Hertz, R., and Spender, C. B.: Effects of methotrexate upon choriocarcinoma and chorioadenoma, Proc. Soc. Exp. Biol. Med. 93:361, 1956.

- 3. Hammond, C. B., Borchert, L., Tyrey, L., Creasman, W. T., and Parker, R. T.: Treatment of metastatic irophoblastic disease: Good and poor prognosis, A. J. Obstet. Gynecol. 115:451, 1973.
- OBSTET. GYNECOL. 115:451, 1973.

  4. Bagshawe, K. D.: Treatment of trophoblastic tumors, Am: Acad. Med. (GB) 5:273, 1976.
- Hammond, C. B., and Suciu, T. N.: Preferable management of gestational trophoblastic disease, Controversy OB-Gyn (In press).
- Vaitukaitis, J. L., Braunstein, G. B., and Ross, G. T.: A radioimmunoassay which specifically measures human chorionic gonadotropins in the presence of human luteinizing hormone, Am. J. Obstet. Gynecol. 113:751, 1972.
- Hammond, C. B., and Lewis, J. L., Jr.: Gestational trophoblastic neoplasms. in Gynecology and Obstetrics, Hagerstown, Md., 1977, Harper and Row, chap. 37N.
- 8. Hammond, C. B.: Unpublished data.
- 9: Hammond, C. B.: Weed, J. C., Jr., and Currie, J. L.: The role of surgery in the current therapy of gestational trophoblastic disease, Am. J. Obstet. Gynecol. In press.
- Curry, S. L., Hammond, C. B., Tyrey, L., Creasman, W. T., and Parker, R. T.: Hydatidiform mole: Diagnosis, management, and long-term follow-up of 347 patients, Obstet. Gynecol. 45:1, 1975.

#### Copyright information

The appearance of a code at the bottom of the first page of an original article in this Journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc., 21 Congress St., Salem, Mass. 01970, (617)744-3350, for copying beyond that permitted by Section 107 or 108 of the U. S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale. For reprint quantities of 50 or more, please contact Publisher.

Thyroid function in gestational trophoblastic neoplasia: Evidence that the thyrotropic activity of chorionic gonadotropin mediates the thyrotoxicosis of choriocarcinoma

BRUCE C. NISULA, M.D. GEORGE S. TALIADOUROS, M.D.

Bethesda, Maryland

An investigation was made of thyroid function in 20 patients with gestational trophoblastic neoplasia. Two patients were judged to be overtly thyrotoxic on the besis of the symptoms and physical findings; both patients had widely metastatic choriocarcinoma, markedly increased serum T4 levels (21.4 and 27.7  $\mu$ g/100 ml), and extremely high levels of serum human chorionic gonadotropin (hCG) (3,220 and 6,720 IU/ml) relative to those of normal pestation (<100 IU/ml). Three other patients had moderately increased serum T4 levels (13 to 7.1  $\mu$ g/100 ml), moderately increased serum hCG levels (110 to 310 IU/ml), and findings on circal examination which suggested euthyroidism. Using the mouse thyroid bioassay, we found that the biologic characteristics of the thyroid-stimulating factor were those of purified hCG, and that the levels of thyroid-stimulating activity in both serum and urine correlated closely with the levels of hCG. These results provide evidence that the thyroid-stimulating activity intrinsic to the hCG molecule plays the central pathophysiologic role in choriocarcinoma-associated the recoxicosis. (AM. J. OBSTET. GYNECOL. 138:77, 1980.)

It has been well established that symptomatic, overt thyrotoxicosis may occur in association with choriocarcinoma. <sup>1–5</sup> Although there is general agreement that a thyroid-stimulating factor secreted by trophoblastic tissues accounts for the increase in thyroid function, the nature of this thyroid-stimulating factor has been a matter of controversy. In early studies, Odell and coworkers concluded that the thyroid-stimulating factor was not human chorionic gonadotropin (hCG), on the basis of the failure of a crude hCG preparation to manifest thyrotropic activity in the chick thyroid bioassay. In contrast, recent studies have shown that hCG is a thyroid-stimulating factor, at least in the mouse, <sup>7</sup> and that the levels of thyroid-stimulating activity detected

in patients with hydatidiform mole and accelerated thyroid function correlate with the hCG level.8, 9 A detailed study of one patient with hyperthyroidism and choriocarcinoma showed that the substance with thyroid-stimulating activity had many of the properties of hCG.5 In other studies, using human thyroid membranes, Amir and associates 10 concluded that hCG is not the principal thyroid-stimulating factor, but that crude urinary hCG and extracts of molar tissue contain a thyroid-stimulating factor apart from hCG. Because of the controversy concerning whether the hCG molecule or some other factor accounts for the acceleration of thyroid function in patients with metastatic choriocarcinoma, we undertook a study of thyroid function, hCG levels, and thyroid-stimulating factors in a series of 20 patients referred for chemotherapy of gestational trophoblastic neoplasia.

From the Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health.

Received for publication November 5, 1979.

Revised February 29, 1980.

Accepted March 27, 1980.

Reprint requests: Dr. Bruce C. Nisula, Room 10-B-09 Building 10, National Institutes of Health, Bethesda, Maryland 20205.

#### Methods

Radioimmunoassay of serum and urinary hCG. Purified hCG (CR119) obtained from the Center for Population Research, National Institute of Child Health and Human Development, was used as the reference preparation as well as the radioligand in the."

3 Nisula and Taliadouros September 1, 1980 Am. J. Obstet. Gynecol.

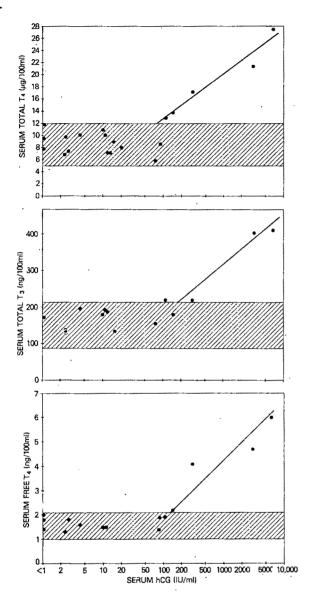


Fig. 1. Serum thyroid function tests in patients with gestational trophoblastic neoplasia as a function of the serum hCG level. The data in the upper, middle, and lower panels show the serum total  $T_4$ , serum total  $T_3$ , and serum free  $T_4$ , respectively. The shaded area in each panel indicates the normal range. For comparison, the serum hCG level in normal gestation rarely exceeds 100 IU/ml.

radioimmunoassays. The biologic potency of hCG CR119 is 13,500 international units per milligram in terms of the 2nd International Standard hCG. Serum hCG was radioimmunoassayed with the use of an antiserum to hCG $\beta$  (SB6). An antiserum to the carboxy-terminal peptide of hCG $\beta$  was used to measure the hCG concentration in kaolin-acetone concentrates of 24-hour urine specimens (level of sensitivity, <0.05 IU/ml) because of the lack of apparent cross-reactivity

by luteinizing hormone in the urine of hypergonadotropic patients.<sup>11</sup>

Tests of thyroid function. Serum  $T_4$  and free  $T_4$  were measured by competitive protein binding assay and dialysis, respectively. Serum  $T_3$  was determined by radioimmunoassay. Serum pituitary thyrotropin (TSH) levels were measured by radioimmunoassay with the use of reagents supplied by the National Pituitary Agency, National Institutes of Health. Normal ranges for the tests of thyroid function were as follows: serum  $T_4$ , 5 to 12  $\mu$ g/100 ml; serum free  $T_4$ , 0.9 to 2.1 ng/100 ml; serum  $T_3$ , 90 to 210 ng/100 ml; serum TSH, 0.5 to 4.5  $\mu$ U/ml; and 24-hour <sup>131</sup>I uptake, 8% to 30%.

Measurement of thyroid-stimulating activity by bioassay. Thyroid-stimulating activity in the sera and kaolin-acetone concentrates of 24-hour urine specimens were measured in the mouse thyroid bioassay as previously described.7 The initial sample of blood was obtained from the infraorbital sinus before the injection of 0.5 ml of serum or urinary concentrate intraperitoneally. Blood was obtained 2, 9, and 22 hours after injection, and the response was calculated as the ratio of the counts per minute at 2, 9, or 22 hours to the initial counts per minute times 100%. In this bioassay, neither the sera nor the urinary concentrates of normal subjects had detectable thyroid-stimulating activity (a response exceeding 200% was defined as detectable). The levels of thyroid-stimulating activity in our patients were referenced to the highly purified hCG (CR119) international reference preparation, which has been shown to contain thyroid-stimulating activity distinctly different from human pituitary TSH and the long-acting thyroid stimulator (LATS). The relative potency estimates were generally determined as the mean of two or more point estimates obtained in separate bioassays. Where feasible, parallel-line potency estimates were made as described previously.7 When the response pattern obtained in the bioassay was typical of that of highly purified hCG (i.e., the peak of the response occurred at 9 hours), the thyroid-stimulating activity was designated hCG-like as opposed to TSHlike or LATS-like, and the thyroid-stimulating potency of the sample was expressed in terms of international units of the hCG (CR119) reference preparation. This permitted a direct comparison of the hCG concentration determined by radioimmunoassay with the hCGlike thyroid-stimulating activity determined by mouse thyroid bioassay.

#### **Patients**

The 20 patients of the present series were referred to the Clinical Center, National Institutes of Health, for

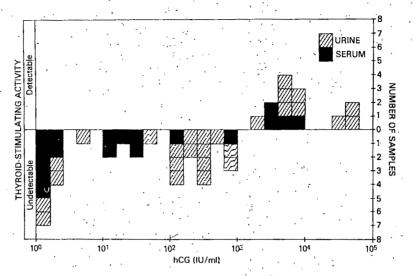


Fig. 2. Classification of the serum samples and unite concentrates of patients with trophoblastic neoplasia according to whether a thyroid stimulating factor was detectable in the mouse thyroid bioassay.

chemotherapy of gestational trophoblastic neoplasia. No patient who was undergoing initial treatment for hydatidiform mole was included in this study, although many of our patients had a history of a prior molar pregnancy. The chemotherapeutic approach to the treatment of these patients with gestational trophoblastic neoplasia was that outlined by Ross and associates. The decision to discontinue chemotherapy was made when the serum hCG level was undetectable (<5 mIU/ml) for three consecutive weeks in a conventional radioimmunoassay with the use of an antiserum to hCGβ.

#### Case reports

Patient 1, a 29-year-old woman, was admitted in April, 1974, for further treatment of metastatic choriocarcinoma. In 1971, a pregnancy was complicated by the development of hydatidiform mole, which was treated by curettage. She was well until February, 1974, when a nodule was excised from the middle lobe of the right lung. The nodule was metastatic choriocarcinoma, and the patient was referred for further treatment. The findings of the physical examination were unremarkable, except for the thoracotomy scar. Serum hCG was undetectable, and the serum T, and T3 were, respectively, 5.8  $\mu$ g/100 ml and 179 ng/100 ml. Subsequently, she developed recurrence of the choriocarcinoma, which proved to be resistant to a variety of chemotherapeutic regimens. From November, 1974, tc August, 1977, the serum hCG levels varied from undetectable to as high as 14 IU/ml. In late August, 1977, the patient was feeling well, the pulse rate was 84 beats per minute, the thyroid gland was normal in size and texture, the serum hCG was 81 IU/ml, and the serum

 $T_4$  was 11.4  $\mu$ g/100 ml. By mid-September, the serum nCG was 340 IU/ml, multiple lung metastases were evident in the chest roentgenogram, and liver metastases were apparent by liver scan and ultrasound. Hyperthyroidism was now chemically evident, but the patient was not yet symptomatic. The serum T<sub>4</sub>, free T<sub>4</sub>, and  $T_3$  were, respectively, 22.8  $\mu$ g/100 ml, 3.9 ng/100 ml, and 350 ng/100 ml. Over the next 2 weeks, the patient lost 4 pounds of weight despite having an increased appetite and feeling quite well. By early October, she had developed clinically overt thyrotoxicosis. She complained of anxiety, palpitations, and insomnia. In addition, there was altered tolerance to heat and a loss of weight. Physical examination showed that the blood pressure was 110/60 mm Hg, and the pulse rate was 108 beats per minute. There was a small, diffuse goiter. The skin was warm and moist, and the eyes showed a stare, but no infiltrative ophthalmopathy. The serum hCG, T<sub>4</sub>, free T<sub>4</sub>, and T<sub>3</sub> were, respectively, 6,720 IU/ml, 27.7 µg/100 ml, 6.05 ng/100 ml, and 407 ng/100 ml (Fig. 1). Serum TSH was undetectable (<0.3  $\mu$ U/ml), and it failed to increase after the administration of thyrotropin-releasing factor (TRF). The 24hour <sup>131</sup>I uptake was 33% (normal, 8% to 30%). The patient was given prophylthiouracil and propanolol. The widely metastatic choriocarcinoma continued to advance, and 2 weeks later she developed gastrointestinal bleeding. Shortly thereafter, she died of a ruptured hepatic metastasis.

Patient 2, a 19-year-old woman, was admitted in May, 1974, with a chief complaint of vaginal bleeding. She had been delivered of a hydatidiform mole 4 months earlier in another hospital, but had not sought further medical attention for this problem until 4 days prior to admission here, when she complained of lower

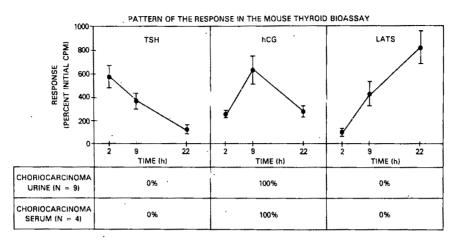


Fig. 3. Pattern of the mouse thyroid bioassay response obtained with the thyroid-stimulating factor in the serum and urine concentrates of the patients with gestational trophoblastic neoplasia (choriocarcinoma) and increased thyroid function. The response patterns obtained with pituitary TSH, highly purified hGG, and the long-acting thyroid stimulator (LATS) are shown in the upper panels.

abdominal pain and vaginal bleeding. She had lost about 40 pounds of weight and complained of episodes of shortness of breath, chest pain, and hemoptysis. In addition, she had been troubled by headaches; these usually occurred in the morning and were often severe enough to keep her in bed. Physical examination showed a blood pressure of 130/60 mm Hg, a pulse rate of 120 beats per minute, and a respiratory rate of 20 per minute. The patient was anxious and appeared to be thyrotoxic. The thyroid gland was soft, diffusely enlarged, and estimated to be twice the normal size. The uterus was palpable midway between the pubis and the umbilicus. There was a fine tremor of the outstretched hands. Although the deep tendon reflexes were normal and symmetrical, there was an abnormal Babinski reflex on the right. The findings of the remainder of the neurologic examination were normal. The chest roentgenogram showed extensive bilateral pulmonary nodular lesions typical of choriocarcinoma. The hematocrit was 33.1%. Serum hCG was 3,220 IU/ml, and the serum T<sub>4</sub>, free T<sub>4</sub>, and T<sub>3</sub> were, respectively, 21.4  $\mu$ g/100 ml, 4.7 ng/100 ml, and 403 ng/100 ml (Fig. 1). Serum pituitary TSH was undetectable, and it failed to increase after the administration of TRF. The patient was treated with five separate 5-day courses of actinomycin D in a dose of 10 µg/kg/day over the next 10 weeks. Because of evidence of brain metastases, she was also given 2,000 rads of brain irradiation over a period of 14 days. Both the choriocarcinoma and the hyperthyroidism responded rapidly. Ten days after the start of chemotherapy, the serum hCG,  $T_4$ , free  $T_4$ , and  $T_3$  were, respectively, 190 IU/ml,  $13.8 \mu g/100 \text{ ml}$ , 2.6 ng/100 ml, and 340 ng/100 ml. After 20 days, the patient was normal by physical examination, and the serum hCG, T<sub>4</sub>, and free T<sub>4</sub> were, respectively, 26 IU/ml, 6.9  $\mu$ g/100 ml, and 1.2 ng/100 ml. Four months later, she felt well and ap-

peared to be euthyroid, and the hCG was undetectable. The serum  $T_4$ , free  $T_4$ , and  $T_3$  were, respectively, 5.5  $\mu g/100$  ml, 1.4 ng/100 ml, and 131 ng/100 ml. The serum TSH level increased from 2.7 to 11  $\mu$ U/ml after the administration of TRF. Over the ensuing 18 months there was no recurrence of the choriocarcinoma and the patient remained euthyroid.

Patients 3, 4, and 5, who ranged in age from 21 to 25 years, were admitted for treatment of gestational trophoblastic neoplasia. Their initial serum hCG levels were in the range of 110 to 310 IU/ml. Serum  $T_4$  levels were moderately increased (13.0 to 17.1  $\mu$ g/100 ml), and  $T_3$  and free  $T_4$  levels were variably increased (Fig. 1). However, these patients were euthyroid as judged by history and physical examination. Pulmonary metastases were present in one patient. In each case, thyroid function tests returned to normal in association with successful chemotherapy of the trophoblastic disease.

Patients 6 through 20, who ranged in age from 18 to 29 years, were admitted for treatment of gestational trophoblastic neoplasia. These patients were euthryoid as judged by history and physical examination, and thyroid function tests were normal (Fig. 1). The serum hCG levels ranged from 0.1 to 95 IU/ml prior to the initiation of chemotherapy.

#### Results

### Thyroid hormone level as a function of serum hCG

level. The relationship between serum hCG level and thyroid function, as determined when the disease was most active in our patients, is shown in Fig. 1. Serum T<sub>4</sub>, free T<sub>4</sub>, and T<sub>3</sub> were normal in the 15 patients whose serum hCG level was less than 100 IU/ml. The peak level of serum hCG rarely exceeds 100 IU/ml during normal gestation. Increased peripheral thyroid hormone levels were apparent only in those five pa-

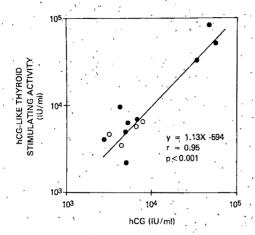


Fig. 4. Correlation of the levels of hCG with the levels of hCG-like thyroid-stimulating activity in the serum and urinary concentrates obtained from the patients with gestational trophoblastic neoplasia and increased thyroid function.

tients whose serum hCG levels exceeded 100 IU/ml. Moreover, in those five patients, the degree of thyroid hyperfunction correlated closely with the serum hCG level (Fig. 1); the patients with the higher levels of hCG had the higher levels of serum T<sub>3</sub> and T<sub>4</sub>. Signs and symptoms of thyrotoxicosis were apparent only in the two patients with the highest serum hCG levels (i.e., Patients 1 and 2).

Detection and characterization of the thyrotropic factor. Using the mouse thyroid bioassay, we examined 27 urine kaolin-acetone concentrates and 18 unextracted serum samples, which were obtained from 16 of the patients with trophoblastic neoplasia, for the presence of a thyroid-stimulating factor. There was detectable thyroid-stimulating activity in nine of the urine concentrates and four of the serum samples (Fig. 2). Notably, the levels of hCG in all of these 13 specimens exceeded 2,000 IU/ml. No urine concentrate or serum sample which contained less hCG than 2,000 IU/ml had detectable thyroid-stimulating activity. No specimen which contained more hCG than 2,000 IU/ml had undetectable thyroid-stimulating activity. The serum samples and kaolin-acetone urine concentrates of four pregnant subjects also had levels of thyroid-stimulating activity below and detection limit of the bioassay.

The qualitative nature of the thyroid-stimulating factor present in these 13 specimens, from our choriocarcinoma patients with accelerated thyroid function, was compared to that of TSH, hCG, and LATS. In the mouse thyroid bioassay, each of these thyroid-stimulating factors evoked a unique time course of the response (Fig. 3). The peak of the response obtained with purified hCG occurred at a time intermediate between that of TSH and that of LATS. Uniformly, the qualitative nature of the thyroid-stimulating factor detected in

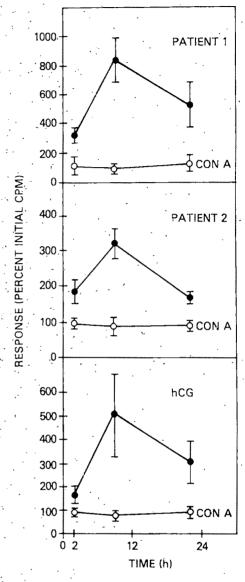


Fig. 5. Adsorption of the thyroid-stimulating factor to the lectin concanavalin A (Con A). Responses obtained in the mouse thyroid bioassay with urine concentrates from Patient 1 and Patient 2 are shown in the upper two panels, and the response with a crude commercial hCG preparation obtained from the urine of pregnant women is shown in the bottom panel. The solid circles indicate samples incubated with Sepharose 4B, whereas the open circles indicate samples incubated with Sepharose 4B to which concanavalin A was covalently linked.

our patients was identical to that of purified hCG (Fig. 3). Equally important was the finding that the level of the hCG-like thyroid-stimulating activity in the patients' sera and urines correlated closely with the level of hCG in these specimens (r = 0.95; p < 0.001) (Fig. 4). No thyroid-stimulating factor other than the hCG was apparent. Therefore, on the basis of both quantitative and qualitative findings, the thyroid-stimulating factor in these specimens was the hCG itself.

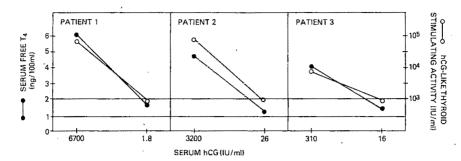


Fig. 6. Serum free  $T_4$  and urinary hCG-like thyroid-stimulating activity levels in Patients 1, 2, and 3 measured in a phase of the patient's illness when the serum hCG level was its highest, and in a phase when the serum hCG level was much lower. The shaded area indicates the normal range for the serum free  $T_4$  levels and the undetectable range for hCG-like thyroid-stimulating activity in the mouse thyroid bioassay.

Table I. Clinical characteristics of patients with choriocarcinoma who were judged to be overtly thyrotoxic

Case No.	Authors (reference)	Patient age (yr)	Tachycardia	Goiter	Lung meta:tases	hCG levels greater than those of pregnancy	Serum T <sub>4</sub>	Increased free T <sub>4</sub>	Serum T <sub>3</sub> (ng/100 ml)	<sup>131</sup> I uptake (% dosel 24 hr)
1.	Smiley and Clements <sup>1</sup>	27	+	+	estical.	+	NA*	NA	NA	NA
2.	Meyers <sup>2</sup>	34	+	+		+	24.3	NA	NA	62.5
3.	Cohen and Utiger <sup>3</sup>	18	+	· +	+	+	>20	NA	NA	64
4.	Morley et al.4	33	+	-	+	+	25	+	232	80
5.	Morley et al.4	19	+	+	+	+	18.8	. +	270	50
6.	Morley et al.4	28	+		+	+	22.3	+	517	54
7.	Cave and Dunn <sup>5</sup>	15	+	+	+	, <b>+</b>	24.7	+	875	NA
8.	Present report	19	· +	+ .	+	+	21.4	+	403	NA
9.	Present report	29	+	+	+	+	27.7	+	407	33

<sup>+ =</sup> yes; - = no.

There were sufficient levels of thyroid-stimulating activity in the urine concentrates of Patient 1 and Patient 2 to permit further comparison of the chemical nature of the thyroid-stimulating factor to that of hCG. Glycoprotein hormones, such as hCG and TSH, will bind to the plant lectin, concanavalin A, covalently linked to Sepharose 4B. As shown in Fig. 5, the thyroid-stimulating factor in the urine of these patients adsorbed to the concanavalin A, as would be expected if the thyroid-stimulating factor were the hCG, itself.

Concordance of hyperthyroidism and the thyroidstimulating factor. To examine the relationship between the levels of the thyroid-stimulating factor in the urine concentrates and the increase in thyroid function in our individual patients, we measured serum free T<sub>4</sub> levels and urinary hCG-like thyroid-stimulating activity levels in Patients 1, 2, and 3, at the time when the tumors were evidently most active, and at another time when the tumors were responding to therapy. As shown in Fig. 6, in each of these patients the acceleration of thyroid function was associated with detectable levels of hCG-like thyroid-stimulating activity. Appropriately, when thyroid function was normal, no bioassayable thyroid-stimulating factor was detected in the urine concentrates, and the hCG levels were correspondingly reduced.

#### Comment

Syndrome of overt thyrotoxicosis in choriocarcinoma. Clinically overt thyrotoxicosis in association with metastatic choriocarcinoma is an uncommon, but well-established syndrome. Including Patients 1 and 2 from the present series, nine reported cases are available for analysis. <sup>1-5</sup> The clinical characteristics of these patients are summarized in Table I. The mean age of these women was 25 years, with a range from 15 to 34 years. In addition to classic signs and symptoms of the thyrotoxic state, such as tachycardia and nervousness, these patients had markedly increased total serum thyroid hormone levels and correspondingly increased free T<sub>4</sub> levels. Uptake of radioactive iodine by the thyroid was increased in all the patients in whom it was examined. Basal TSH levels were not only below nor-

<sup>\*</sup>NA indicates not available.

mal, but they were undetectable, and the TSH response to the administration of TRF was suppressed. Most of these patients had a small, diffuse goiter, and none had the infiltrative eye signs associated with Graves' disease. Among patients with gestational trophoblastic neoplasia, this group of patients stands out because of the extent of their disease. All of these patients had widely metastatic disease, invariably manifest by multiple lung metastases. Also signaling a large tumor burden was the presence of extremely high levels of serum hCG, exceeding those of normal pregnancy, often by a considerable degree. For example, in our two patients, the serum hCG levels were more than 30-fold the maximal level observed in normal pregnancy. Consequently, this unusual form of thyrotoxicosis is easy to recognize because of the distinctive clinical setting in which it occurs and the remarkable levels of hCG present in the serum.

The clinical course of the thyrotoxicosis in this syndrome invariably follows the clinical course of the underlying choriocarcinoma. Our Patients 1 and 2 illustrate the two established patterns of the natural course of the disease. Patient 1 was euthryoid when initially seen, but became thyrotoxic later as the malignancy progressed. Patient 2, on the other hand, presented with extensive metastatic choriocarcinoma and thyrotoxicosis, both of which responded rapidly to chemotherapy directed toward the cancer. It is evident that treatment with antithyroid drugs and propanolol, rather than radiotherapy or surgical intervention, is the appropriate management of the thyroidal complications of metastatic choriocarcinoma. Ablative therapy is contraindicated because the thyrotoxicosis is cured with remission of the underlying disease.

A review of the literature gives the impression that covert hyperthyroidism (increased thyroid function without signs and symptoms of thyrotoxicosis) occurs somewhat more frequently than overt hyperthyroidism in patients with gestational trophoblastic neoplasia. In our series of 20 patients, there were three with covert hyperthyroidism, two with overt hyperthyroidism, and 15 with normal thyroid function. Odell and associates<sup>6</sup> reported seven patients with covert hyperthyroidism, and Miyai and associates9 and Dowling and associates13 reported another two cases each. Furthermore, in hydatidiform mole, not only is thyroid hyperfunction common, but it is also probably somewhat more common than in choriocarcinoma. However, as with choriocarcinoma, most of the affected patients have been found to be covertly hyperthyroid rather than overtly thyrotoxic.8, 9, 13 The reason remains unknown for this disparity between thyroid function tests and clinical status in patients with the several different types of gestational trophoblastic disease. However, it is clear from our study and that of Miyai and associates9 that one cannot account for this discrepancy on the basis of rhibition of T<sub>4</sub> and T<sub>3</sub> conversion. Also, it does not appear to be due to resistance to the action of thyroid hormones, at least at the level of the pituitary. The TSH response to TRF is appropriately suppressed.9 Our experience would suggest that the patients with evert hyperthyroidism simply have not had serum tayroid hormone levels sufficiently elevated for a long enough period of time to develop clinically overt thyrotoxicosis. In the present series, thyroid hormone Evels were quite a bit lower in the three patients with covert hyperthyroidism than in the two patients with overt hyperthyroidism. Furthermore, Patient I was oberved to be covertly hyperthyroid for a period of time before becoming overtly thyrotoxic. Thus, there is evidence to suggest that the overt and covert thyroid hyperfunction are parts of a continuum rather than separate entities.

Pathogenesis of thyroid hyperfunction in choriocarcinoma. Our clinical observations of the present series of 20 patients with gestational trophoblastic neoplasia suggest that the thyrotropic activity intrinsic to the hCG molecule could play the central pathophysiologic role in the thyrotoxicosis associated with metastatic choriocarcinoma. Only those patients with the highest levels of hCG were the ones to manifest thyroid hyperfunction; and in each of these patients, the serum hCG level exceeded that seen in normal pregnancy, wherein euthyroidism is the rule. This is in keeping with the rather weak intrinsic thyroidstimulating activity of the hCG molecule. Thus, since the concentration of hCG in the circulation in patients with choriocarcinoma-associated thyrotoxicosis can be of the order of one million times more than the normal TSH concentration, it seems reasonable to postulate that what the hCG lacks in potency as a thyroid stimulator, it more than makes up in concentration. Not only was the thyroid hyperfunction limited to those patients with extremely high levels of hCG, but the degree of thyroid hyperfunction correlated closely with the serum level of hCG. The increase in total T<sub>4</sub> level was paralleled by an increase in the free T<sub>4</sub> level, thus showing that increased binding does not account for the increased total hormone levels. Actually, it has long been known that the thyroid binding globulin concentration is not increased in choriocarcinoma as it is in normal pregnancy13; presumably this relates to the lower estrogen levels in choriocarcinoma.

Laboratory investigation of the thyrotropic factor in • the sera and urines of our patients revealed that its characteristics were those of the hCG molecule, and "

throughout our studies there was no evidence of a thyroid-stimulating factor other than hCG in the thyrotoxic patients. The serum pituitary TSH was suppressed to undetectable levels, as would be expected. Uniformly, the biologic characteristics of the thyroidstimulating activity in the serum and urine of our patients were identical with those of hCG. Thus, as with highly purified hCG, the peak of the response evoked in the mouse thyroid bioassay occurred at a time between that of pituitary TSH and that of LATS. Like hCG, the substance with thyroid-stimulating activity adsorbed to concanavalin A, thus indicating that it is a glycoprotein. Furthermore, the levels of hCG-like thyroid-stimulating activity in both sera and urine correlated closely with the levels of hCG in the samples. These data argue strongly that the thyrotropic factor secreted by gestational trophoblastic neoplasia is, indeed, hCG. However, it should be acknowledged that, in theory, a thyroid-stimulating factor in addition to hCG could contribute to the changes in thyroid function in these patients. This possibility seems rather unlikely for several reasons. First, to account for our correlation between the clinical findings and the hCG levels would require that this putative factor's secretion be closely linked to the secretion of hCG, and that its half-life be quite similar to the half-life of hCG. Second, hCG, pituitary TSH, and LATS exhibit a thyrotropic action on the mouse thyroid. Yet, using the mouse thyroid bioassay, we were unable to find evidence for the presence of a thyroid-stimulating factor in addition to hCG in our patients. It seems unlikely that this putative factor would be less apparent than hCG in the mouse thyroid bioassay, particularly if it is present in sufficient levels to induce hyperthyroidism in our patients. Third, using a highly sensitive TSH radioligandradioreceptor assay, we were unable to find any evidence of a thyrotropic factor other than hCG in the urine of our hyperthyroid patients with choriocarcinoma, or, for that matter, in crude or highly purified hCG preparations.14 Thus, the possibility that trophoblastic tissues secrete biologically significant amounts of a thyrotropic factor other than hCG has become increasingly remote in recent years; but this possibility cannot be categorically excluded on the basis of the available data.

It is evident that the finding that hCG is thyrotropic in mice7 is consistent with, but not proof of, hCG being thyrotropic in man. Indeed, in one other species, the chicken, hCG has been reported to lack thyrotropic activity.6 Therefore, several groups of investigators have examined the effects of hCG on the human thyroid. Silverberg and associates<sup>15</sup> showed that a crude hCG preparation activated adenylate cyclase in human thyroid tissue slices, and Sowers and associates<sup>16</sup> used a crude hCG preparation to stimulate thyroidal iodine release in men, but since purified hCG was not used in these studies, one could not be sure whether the hCG molecule or some other putative thyrotropic factor in the crude hCG preparation accounted for the observed effects. More recently, we have shown that highly purified hCG stimulates adenylate cyclase activity in purified human thyroid membranes, and that the hCG molecules in crude hCG account for its human thyrotropic activity (Carayon, Lefort, and Nisula, unpublished observations). Considered together, these observations clearly indicate that hCG has a thyrotropic action on the human thyroid and, thereby, contribute valuable support to the postulated role of hCG in the mechanism of choriocarcinoma-associated thyrotoxicosis.

In summary, there is a rather sizable body of clinical evidence, derived from studies of gestational trophoblastic diseases, choriocarcinoma, and hydatidiform mole, and laboratory evidence, obtained with the mouse thyroid bioassay and human thyroid tissue, which support a central pathophysiologic role for the hCG molecule in the acceleration of thyroid function which occurs in patients with trophoblastic diseases. The data base for this concept comes primarily from the correlation between the hCG level and endogenous thyroid function, and from the observation that hCG has intrinsic thyroid-stimulating activity.

We gratefully acknowledge the assistance of the numerous personnel who cared for these patients on the 12E Ward of the Clinical Center, National Institutes of Health, and the technical assistance of Alexander Antonakos.

#### REFERENCES

- Smiley, I., and Clements, A. B.: Chorioepithelioma of the uterus with thyrotoxicosis, pronounced hormone titer, and death from intra-abdominal hemorrhage, Am. J. Obstet. Gynecol. 43:471, 1940.
- Myers, W. P. L.: An analysis of medical problems in cancer, Med. Clin. North Am. 45:563, 1961.
- Cohen, J. D., and Utiger, R. D.: Metastatic choriocarcinoma associated with hyperthyroidism, J. Clin. Endocrinol. Metab. 30:423, 1970.
- Morley, J. E., Jacobson, R. J., Melamed, J., and Hershman, J. M.: Choriocarcinoma as a cause of thyrotoxicosis, Am. J. Med. 60:1036, 1976.
- 5. Cave, W. T., and Dunn, J. T.: Choriocarcinoma with hy-

- perthyroidism: Probable identity of the thyrotropin with human chorionic gonadotropin, Ann. Intern. Med. 85: 60, 1976.
- Odell, W. D., Bates, R. W., Rivlin, R. S., Lipsett, M. B., and Hertz, R.: Increased thyroid function without clinical hyperthyroidism in patients with choriocarcinoma, J. Clin. Endocrinol. Metab. 23:658, 1963.
- 7. Nisula, B. C., Morgan, F. J., and Canfield, R. E.: Evidence that chorionic gonadotropin has intrinsic thyrotropic activity, Biochem. Biophys. Res. Commun. **59**:86, 1974.
- 8. Higgins, H. P., Hershman, J. M., Kenimer, J. G., Patillo, R. A., Bagley, T. A., and Walfish, P.: The thyrotoxicosis of hydatidiform mole, Ann. Intern. Med. 84:307, 1975.
- Miyai, K., Tanizawa, D., Yamamoto, T., et al.: Pituitarythyroid function in trophoblastic disease, J. Clin. Endocrinol Metab. 42:954, 1976.
- docrinol. Metab. 42:254, 1976.

  10. Amir, S. M., Sullivan, R., and Ingbar, S. H.: Studies in human thyroid membranes indicating that hCG is not the thyroid stimulator of molar pregnancy, Program of the 53rd Annual Meeting of the American Thyroid Association, 1977, p. T-8. (Abstr.)
- 11. Ayala, A. R., Nisula, B. C., Chen, H-C., Hodgen, G. D., and Ross, G. T.: Highly sensitive radioimmunoassay for

- chorionic gonadotropin in human urine, J. Clin. Endocrinol. Metab. 47:767, 1978.
- Z. Ross, G. T., Goldstein, D. P., Hertz, R., Lipsett, M. B., and Odell, W. D.: Sequential use of methotrexate and actinomycin D in the treatment of metastatic choriocarcinoma and related trophoblastic diseases in women, Am. J. OBSTET. GYNECOL. 93:223, 1965.
- 3. Lowling, J. T., Ingbar, S. H., and Freinkel, N.: Iodine metabolism in hydatidiform mole and choriocarcinoma, J. Clin. Endocrinol. Metab. 20:1, 1960.
- 14. Davies, T. F., Taliadouros, G. S., Catt, K. J., and Nisula, B. C.: Assessment of urinary TSH-competing activity in choriocarcinoma and thyroid disease: Further evidence for hCG interacting at the thyroid cell membrane, J. Clin. Endocrinol. Metab. 49:353, 1979.
- Silverberg, J., O'Donnell, J., Sugenoya, A., Row, V. V., and Volpe, R.: Effect of human chorionic gonadotropin on human thyroid tissue in vitro. J. Clin. Endocrinol. Metab. 46:420, 1978.
- Sowers, J. R., Hershman, J. M., Carlson, H. E., and Pekary, A. E.: Effect of hCG on thyroid function in euthyroid man, J. Clin. Endocrinol. Metab. 47:898, 1978.

## Tubal lesions subsequent to sterilization and their relation to fertility after attempts at reversal

GLORIA VASQUEZ, M.D.
ROBERT M. L. WINSTON, M.D., M.R.C.O.G.\*
WILLY BOECKX, M.D.
IVO BROSENS, M.D., Ph.D.
Leuven, Belgium

Tubal biopsy specimens were obtained at the time of tubal anastomosis in 26 previously sterilized women. Scanning electron microscopy showed that half the patients had abnormalities of tubal mucosa, including loss of mucosal folds, deciliation, and polyposis. These pathologic conditions, the morphologic features of which we describe, significantly increase in incidence the longer the time after sterilization. Our evidence suggests that the soorer reversal is performed after sterilization the greater the chance of a successful intrauterine pregnancy. (Am. J. Obstet. Gynecol. 138:86, 1980.)

THE INCREASING demand for reversal of sterilization has stimulated the development of microsurgical techniques.<sup>1</sup> Preliminary reports<sup>2, 3</sup> indicate that the pregnancy rate after microsurgical anastomosis is double that achieved after most conventional methods.<sup>4</sup> However, the pregnancy rate is not so high as the patency rate, the incidence of tubal pregnancy is still elevated, and pregnancy may occur only many months after the operation. It is possible that these disturbances in fertility could be related to tubal damage subsequent to sterilization.

In this study, the morphologic features of the mucosa of the fallopian tubes were evaluated in a series of sterilized patients who underwent reversal operations. As controls, tubes were taken from fertile women undergoing hysterectomy for gynecologic reasons.

> From the Unit for the Study of Human Reproduction, Academic Hospital St. Rafaël.

This study was supported by a grant from 3rd Cycle Funds of the University of Leuven.

Received for publication July 19, 1979.

Revised March 17, 1980.

Accepted March 27, 1980.

Reprint requests: Ivo A. Brosens, Ph.D., Department of Obstetrics and Gynecology, Academic Hospital St. Rafaël, Leuven, Belgium.

\*Recipient of a grant from the 3rd Cycle Funds of the University of Leuven and from the Wellcome Foundation. Present address: Hammersmith Hospital, London, W12, United Kingdon.

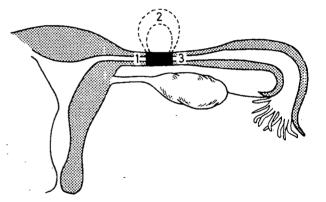


Fig. 1. Scheme of sterilized oviduct showing the different sites of biopsy. 1, Segment adjacent to the tubal occlusion on the uterine side. 2, Blind loop of sterilized segment. 3, Segment adjacent to the tubal occlusion on the ampullary side.

#### Material and methods

Twenty-six sterilized patients were investigated at the time of reversal operation. Similar biopsy specimens of the tubes were also taken from eight patients undergoing hysterectomy, and these served as controls. All sterilized patients had regular cycles, but some of the control patients had menorrhagia. Sterilized patients were between 28 and 42 years old at the time of operation and had been sterilized 1 to 11 years before. The technique of sterilization included catgut ligature with section, electrocoagulation, or use of the Falope ring. The latter method has been used in our patients for only about 2 years. The site of sterilization in all

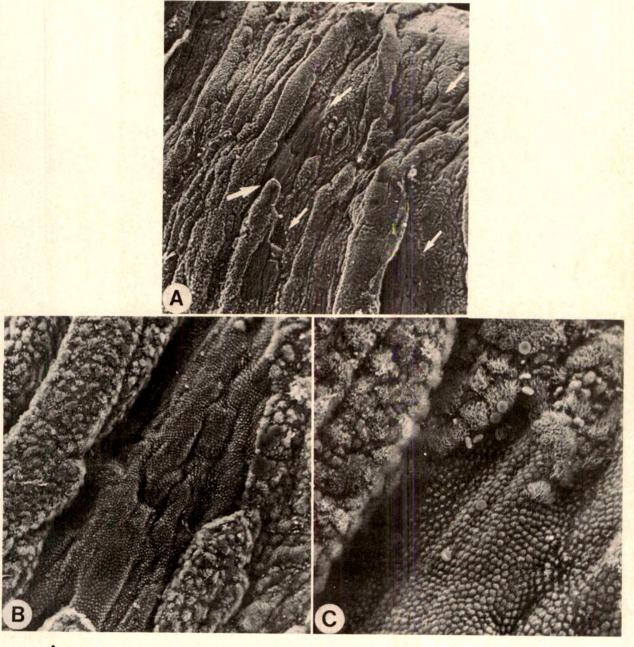


Fig. 2. Site 1, corresponding to isthmus, 7 years after postpartum ligature. A, Four parallel attenuated folds were present on the entire length of the biopsy specimen. A fifth fold ended in the middle of the specimen (large arrow). Note the pattern of distribution of ciliated cells (speckled gray-white) and four circumscribed areas of deciliation (small arrows). (×60.) B, Enlargement of deciliated area situated just above the interrupted fold. Note complete absence of ciliated cells. The surrounding epithelium is uniformly well ciliated. (×250.) C, Enlargement of the same deciliated area, showing the abrupt change from completely deciliated to well-ciliated epithelium. The cells in this area have a rounded surface membrane covered by microvilli with single cilium. A few surface-contaminating red blood cells are seen. (×620.)



**Fig. 3.** Site 1, corresponding to isthmus, 8 years after ligature sterilization. Finger-like polyp is oriented parallel to the folds and directed toward the fimbriae. The surface is covered by ciliated and nonciliated cells, similar to the mucosa of the folds. Although the isthmus is patent, the polyp intrudes into the lumen. (×100.)

patients was the isthmus, and included at least the beginning of the ampullary segment in half the patients. In each case, at least one biopsy specimen was taken which included a complete transverse section of the luminal surface of the tube near the site of interruption (Fig. 1).

All specimens were immediately opened longitudinally under the operating or dissecting microscope to expose the tubal lumen, fixed by submersion in 5% buffered glutaraldehyde, and prepared for scanning electron microscopy (SEM).<sup>5, 6</sup> After SEM, selected biopsy specimens were embedded in Epon, and semiserial 1-micron sections were examined under the light microscope.<sup>7</sup> After reversal of sterilization, all the patients in this study were followed for a minimum of 1 year and for as long as 3 years.

#### Results

Since our object was to study only patients with patent tubes who sometimes failed to conceive after reversal sterilization had been attempted, the complete tubal mucosa of our patients, ideally, should have been assessed and compared with the normal. Clearly, this was not feasible, and in actual fact the major mucosal lesions were largely confined to site 1 shown in Fig. 1, so that details are given only for that site.

Site 1. This segment, adjacent to the site of sterilization, corresponded to the isthmus in most patients, but in four it was from the lateral part of the cornu. When the biopsy specimens were mounted under the stereomicroscope (×10 to ×40) before sputtering, flattening of the folds was clearly evident in 18 of 26 specimens. The most interesting finding was the presence of polyps arising from the top of the folds. SEM showed that the folds were attenuated and covered with ciliated and nonciliated cells. In 10 specimens, clearly outlined, sharply demarcated areas of deciliation were present, measuring 60 to 130 microns and 150 to 180 microns. In three specimens, there areas were immediately adjacent to a polyp. The cells in these deciliated areas were covered by microvilli, and many had a single cilium (Fig. 2). Polypoid formations were present in 14 specimens. They were either rounded or fingerlike in shape and measured 40 to 635 microns in height and 25 to 370 microns in width. They were either oriented vertically toward the lumen or followed the direction of the folds (Fig. 3). The smallest polyps were found in association with multiple polyps (Fig. 4). No gland openings were seen on the surface of the polyps. After scanning, five biopsy specimens with polyps were serially sectioned and 1-micron sections were stained with methylene blue. The polyps consisted of stromal tissue covered by essentially normal epithelium (Fig. 5). However, in one polyp a glandular structure was present with features that suggested endometrial origin or endometrial metaplasia. All lesions (flattening of folds, deciliation, and polyps) were most common in patients who had been sterilized for more than 5 years, were uncommon in patients who had been sterilized for 3 or 4 years, and were absent in patients who had been sterilized for a shorter period (Table I).

In control specimens, the mucosa showed normal numbers of ciliated and nonciliated cells, no flattening of folds, and no polyps. This was irrespective of the stage in the menstrual cycle, and we have previously shown that optical changes in tubal ciliation are minimal.<sup>8</sup>

Site 2. This segment, a blind loop at the site of sterilization, was present in the tube with a Falope ring and in five doubly ligated oviducts. On the ringed oviduct, the lumen was difficult to identify. Low-power examination of the other loops revealed a dilated lumen with a completely flattened epithelial surface. SEM showed mainly nonciliated cells which were pleomorphic and often appeared stretched and swollen with a rounded surface membrane, giving a "cobblestone" appearance. Fine microvilli covered most of them. Areas with a cell with a single cilium were common. Ciliated cells were

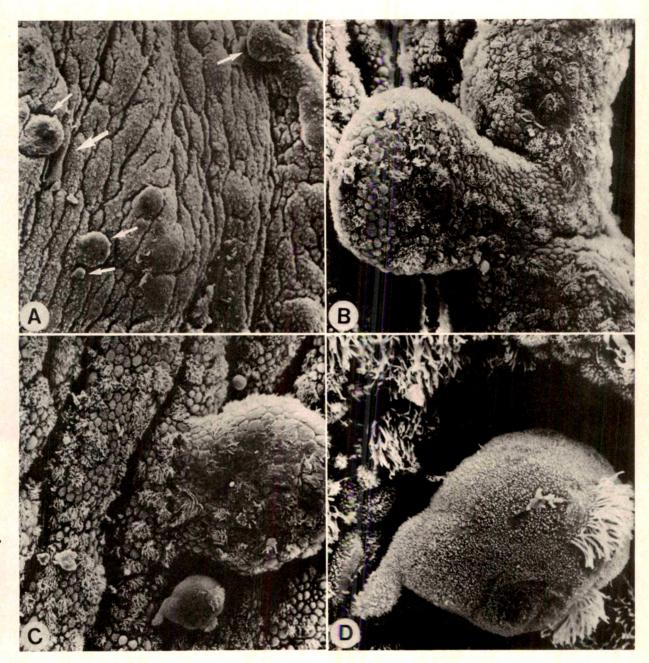


Fig. 4. Site 1, corresponding to isthmus, ligated 5 years before at the time of contralateral tubal pregnancy. A, The longitudinally opened lumen shows very much attenuated folds. Four rounded polyps (small arrows) and one deciliated area next to one of the polyps (large arrow) are present.  $(\times 110.)$  B, Enlargement of upper right corner of A. Rounded polyp arising from the top of a fold; surface covered by ciliated and nonciliated cells, continuous with the epithelium which covers the fold. (×520.) C, Enlargement of lower left corner of A. The bigger polyp shows ciliated and nonciliated epithelium. In the center of this polyp the cell boundaries are not clear, probably because of inadequate washing. The small polyp is pedunculated; cell boundaries are not apparent. (×540.) D, Enlargement of C showing the surface with no clear cell boundaries. The bulk of the surface is covered by microvilli, but there are a few ciliated cells. (×2,200.)

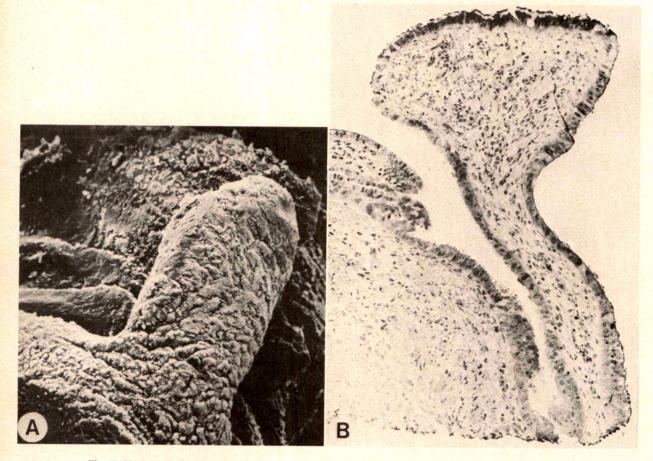


Fig. 5. Site 1, isthmus 7 years after postpartum ligature. A, A polyp arising from one of the folds traverses the lumen perpendicularly to the direction of the folds. Its surface is covered by ciliated and nonciliated epithelium. ( $\times$ 115.) B, Section of the polyp shown in A. A fine layer of gold from the sputtering of the biopsy specimen covers the previously scanned surface. The polyp has a predominantly tall ciliated and nonciliated epithelium, with stratification at its base and a nonglandular stroma. (1-micron section, methylene blue,  $\times$ 205.)

very sparse (<5% of cells). No polyps were found in these biopsy specimens.

**Site 3.** This biopsy site corresponded to the ampulla or to the ampulla-isthmus junction in all except three specimens, in which it corresponded to the isthmus. A normal fold pattern was present in all biopsy specimens. The surface epithelium had a normal ratio of ciliated cells. None of these specimens had polypoid formations.

Fertility subsequent to reversal attempt. Table II summarizes the clinical data and fertility after operations for reversal of sterilization, relative to the time interval elapsing between sterilization and tubal anastomosis.

#### Comment

Scanning electron microscopy revealed that patients who have been sterilized, may develop flattening of folds, deciliation, and polyposis in the fallopian tubes. The polyps that we observed were generally small, varying in size from 40 to 635 microns at their largest diameter. Therefore, it is not surprising that these polyps were not diagnosed by routine preoperative hysterosalpingography performed before some of the reversal operations, but they could be easily seen with the operating or dissecting stereomicroscope at a magnification of  $20\times$  to  $40\times$ . The covering epithelium was composed of ciliated and nonciliated cells and was not different from the surrounding tubal epithelium. To our knowledge, this is the first report of tubal polyps after sterilization. Intramural polyps have been described<sup>9, 10</sup> and have been said to cause infertility<sup>11</sup> if they are bilateral.

Until more detailed investigations are undertaken, the histogenesis of these polyps must remain speculative, but certain observations are permissible. The fact

Table I. Isthmic tubal lesions subsequent to sterilization

Years poststerilization	Number of patients (n)	Age (Mean ± SD)	Flattening of folds (n)	Deciliation (n)	Polyps (n)
More than 5	15	33.4 ± 3.4	14*	8†	11*
3 to 4	7	$32.5 \pm 1.7$	4†	2	4†
Less than 3	4	$32.0 \pm 0.7$	0	0	0
Controls	8	$36.1 \pm 6.5$	0	0	. 0

<sup>\*</sup>P < 0.005 controls.

Table II. Clinical data and fertility outcome

	Sterilization-reversal interval		
	Less than 5 yr	More than 5 yr	
Number of patients	11	15	
Technique of sterilization			
Surgical	7	11	
Electrocoagulation	2	٦l	
Falope ring	1	<del></del>	
Unknown	1	3	
Age at reversal (range in years, mean $\pm$ SD)	$29-35(31.7 \pm 1.9)$	$27-42(33.4 \pm 3.4)$	
Patients with intrauterine pregnancy			
Number (percentage)	7 (63%)	5* (30%)	
Interval (months) from reversal to pregnancy	3-5	2-8	
Patients with tubal pregnancy			
Number	. 1	0	
Interval after operation (months)	22		

<sup>\*</sup>Two patients underwent first-trimester abortion.

that polyps were found only in women who had been sterilized for at least 3 years clearly suggests that a time factor is involved. It is possible that the polyps derive from aberrant regenerative processes after occlusive damage to the tubes. Some of the polyps arose on normal mucosal folds and were covered by essentially normal tubal mucosa, but most were associated with flattened folds. This suggests that the polyps could be residual foci of normal mucosa on atrophic folds. In support of this view, we have noticed that patients who had been sterilized for a long period before the reversal attempt tended to have a dilated isthmic segment with some hydrosalpinx formation.

When polyps were present, the segment on the uterine side of the ligature was generally distended, and it was invariably this segment that bore the polyps. A hint, and it can be no more than that, that the polyps derive from foci of acquired endometriosis was the finding of endometrium-type epithelium in one example. If Sampson's reflux theory of the genesis of endometriosis is correct, it is scarcely surprising that occlusion of the fallopian tubes could facilitate deposition of endometrial cells in the proximal (uterine) segments, particularly if the tubes are abnormally dilated. Further investigations will be required to determine the histogenesis of these lesions. Our present data are

insufficient to substantiate whether they are related to circumstances at the time of sterilization, such as menstruation, delivery, termination of pregnancy, or to the technique of sterilization. Nevertheless, it is clear that the longer the interval after sterilization, the greater the epithelial changes that we have observed.

Our preliminary follow-up data in the assessment of clinical outcome permit a few tentative conclusions. The shortest time interval so far is I year for two patients, both of whom are now pregnant, and the longest interval is 21/2 years. It would seem that the sooner sterilization is reversed, the more likely the patient is to become pregnant, and that from 5 years onward the success rate rapidly declines. It is of interest that the one instance of tubal pregnancy occurred 22 months after the reversal operation, and it was the only pregnancy in the series which occurred such a long time after the operation. It may be that the development of tubal lesions, such as flattening of mucosal folds, deciliation, and polyp formation, interferes with the normal transport of gametes and, hence, reduces fertility. At present, we believe that these lesions should be considered to be an indication of a disorder of the isthmic portion of the tube associated with chronic occlusion. Of course, at the time of a reversal attempt, biopsy specimens could be taken only from a small ...

<sup>†</sup>P < 0.025 versus.

segment of the tube, so that we are ignorant of the state of the tubal mucosa in general. It should be mentioned that, at the time of operation, the operating microscope is of great help in determining the junction between abnormal and apparently normal mucosa and in identifying mucosal polyps.

We wish to thank Professor W. B. Robertson (London) for his critical advice.

#### REFERENCES

- 1. Brosens, I., and Winston, R. M. L.: Reversibility of female sterilization, London, 1979, Academic Press.
- Gomel, V.: Tubal reanastomosis by microsurgery, Fertil. Steril. 28:59, 1977.
- 3. Winston, R. M. L.: Microsurgical tubocornual anastomosis for reversal of sterilization, Lancet 1:284, 1977.
- 4. Siegler, A. M., and Perez, R. J.: Reconstruction of fallopian tubes in previously sterilized patients, Fertil. Steril. **26:**383, 1975.
- 5. Andersen, T. F.: Techniques for the preservation of three-dimensional structures in preparing specimens for the electron microscope, Trans. N. Y. Acad. Sci. Ser. II,
- 6. Ludwig, H., and Metzger, H.: The human female repro-

- ductive tract. A scanning electron microscopic atlas, Ber-
- lin, 1976, Springer Verlag, p. 3.
  7. Goyens, K.: Post-scanning, T. Belg. Veren. Laboratoriumtechn. 5:141, 1978.
- Brosens, I., and Vasquez, G.: Fimbrial microbiopsy, J. Reprod. Med. 16:171, 1976.
- 9. Lisa, J. R., Gioia, J. D., and Rubin, I. C.: Observations on the interstitial portion of the fallopian tube, Surg. Gynecol. Obstet. **99:**159, 1954.
- 10. Fernström, I., and Lagerlöf, B.: Polyps in the intramural part of the fallopian tubes. A radiographic and clinical study, J. Obstet. Gynaecol. Brit. Commw. 71:681, 1964.
- 11. Bret, A. J., and Grepinet, J.: Polypes andométriaux de la portion intramurale de la trompe. Leur rapport avec la stérilité et l'endométriose, Sem. Hôp. Paris 43:183, 1967.

# Receptor-like binding proteins for testosterone and progesterone in the human ovary

ARIEL MILWIDSKY, M.D.\*
MUAZAZ A. YOUNES, PH.D.
NORMA F. BESCH, PH.D.
PAIGE K. BESCH, PH.D.
RAYMOND H. KAUFMAN, M.D.
Houston, Texas

The presence of two receptor-like proteins in human ovarian cytosol is described, one for testosterone and the other for progesterone. They have high affinity and are saturable, thermolabile, and highly specific. The properties of these proteins are discussed, and their possible role in the regulation of ovarian function is discussed. (Am. J. OBSTET. GYNECOL. 138:93, 1980.)

THE IMPORTANT role of steroid receptors in the mechanism of action of steroid hormones has been recognized during recent years. The ovary is generally considered to have two important functions: ovulation and the secretion of steroid hormones. Progesterone .s not only an important intermediate in steroid synthesis but is also produced in large quantities by the developing corpus luteum. Until very recently, most of the experimental evidence1 indicated that the androgens were produced de novo only in the thecal cells of the human ovary. However, McNatty and associates2 have shown that both cell types in the follicle and the stromal tissue can produce androgens as well as progesterone and estrogen. The various compartments differed not in their steroidogenic capacity but in the patterns of steroidogenesis shown in relationship to follicular growth and atresia. Demonstration of the presence of progesterone and androgen receptors in the human ovary would suggest that ovarian morphologic features

From the Reproductive Research Laboratory, St. Luke's Episcopal Hospital, and the Department of Obstetrics and Gynecology, Baylor College of Medicine.

Received for publication October 5, 1979.

Revised March 21, 1980.

Accepted March 27, 1980.

Reprint requests: Dr. P. K. Besch, Reproductive Research Laboratory, St. Luke's Episcopal Hospital, Houston, Tezas 77030.

\*Work done during the tenure of a Post-Residency Fellowship in the Reproductive Research Laboratory. Present address: Department of Obstetrics and Gynecology, Hadassah University Hospital, Mouni Scopus, Jerusalen, Israel. and/or function is regulated by the ovary's own secretion. Support for the presence of an androgen receptor is provided by the studies of Schreiber and associates,<sup>3, 4</sup> who found a testosterone-binding protein with receptor-like properties in ovaries from estrogen-stimulated, hypophysectomized, immature female rats. Friberg and associates<sup>5</sup> presented evidence that suggested the presence of androgen receptors in four cases of human ovarian tumors. Schreiber and Hsueh<sup>6</sup> and Jacobs and Smith<sup>7</sup> have found progesterone binders with receptor-like properties in the rat ovary and cow ovary, respectively. The purpose of the present study was to investigate the possibility that the human ovary contains high-affinity binders for testosterone and progesterone.

#### Material and methods

The steroids used were: pregn-4-ene-3,20-dione (progesterone); androst-4-ene-17 $\beta$ -ol,3-one (testosterone);  $5\alpha$ -androstan-17 $\beta$ -ol,3-one (dihydrotestosterone—DHT); androst-5-ene-3 $\beta$ ,17 $\beta$ -diol (androstenediol); androst-4-ene-3,17-dione (androstenedione); estra-1,3,5 (10)-triene-3,17 $\beta$ -diol (estradiol);  $17\alpha$ ,21-dimethyl-19-nor-pregn-4,9-diene-3,20-dione (R5020);  $17\alpha$ -methyl androst-1,9,11-triene-17 $\beta$ -ol,3-one (R1881). Progesterone (93 Ci/mmol), R5020 (87.0 Ci/mmol), R1881 (87 Ci/mmol), and testosterone (98.9 Ci/mmol) were purchased from New England Nuclear; radiolabeled DHT (50.6 Ci/mmol) was obtained from Amersham-Searle Corporation. All nonlabeled steroids were purchased from Steraloids, Inc., Wilton, N. H.

Ovaries were obtained from women between the ages of 28 and 40, who underwent unilateral or bilat-

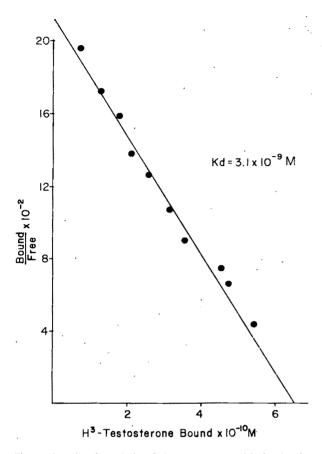


Fig. 1. Scatchard analysis of the testosterone binder in the 35% ammonium sulfate fraction of a single human ovary. Incubations (total volume, 0.6 ml) of increasing amounts of <sup>3</sup>H-testosterone (0.2 to 40 nM) in the presence of 100-fold excess of unlabeled testosterone were performed at 4° C overnight.

eral oophorectomy at Baylor College of Medicineaffiliated hospitals, mainly for the indication of "residual ovary syndrome." The "residual ovary syndrome"8 is a symptom complex in the pelvic area presumably resulting from prior pelvic surgical procedures. The primary symptom is pelvic pain. None of the ovaries used in this study had any type of tumor (functional or nonfunctional). Immediately after the ovaries were removed, they were placed in cold saline solution and transferred to the laboratory, where they were washed several times with cold saline solution to remove the blood. The two final washes were with buffer (10 mM tris-HCl, pH 7.4, with added 1.5 mM ethylenediaminetetra-acetic acid, 12 mM thioglycerol, and 10% glycerol). The tissue was then sliced into small fragments and homogenized by means of a polytron PT-10ST with 3 volumes of buffer. The suspension obtained was then centrifuged at 1,000 g for 15 minutes to sediment nuclei. The supernatant was centrifuged at 105,000 g for 60 minutes, to furnish cytosol

**Table I.** Displacement of <sup>3</sup>H-testosterone from the androgen binder by competing radioinert steroids (expressed in terms of relative binding affinity)

³H-steroid	Competing nonlabeled steroid	Relative binding affinity (%)
Testosterone	Testosterone	. 100
	DHT	77.5
	Androstenediol	18.2
	Androstenedione	3.3
	R5020	< 0.5
	Estradiol	< 3.0

as a clear supernatant. One hundred percent saturated ammonium sulfate was then added dropwise with stirring to the cytosol over 60 minutes to give a final concentration of 35% ammonium sulfate. The resulting precipitate was pelleted by centrifugation, and the supernatant was discarded. The pellet was dissolved in buffer. The fractionated cytosol thus obtained was then stripped of endogenous hormone by a 1-hour incubation with 1 volume of 0.5% dextran-coated charcoal (0.5% charcoal and 0.05% dextran T 70) at 4° C.

Scatchard analyses<sup>10</sup> were performed with the use of <sup>3</sup>H-testosterone (0.2 to 40 nM), <sup>3</sup>H-progesterone (0.4 to 13 nM), <sup>3</sup>H-DHT (0.4 to 22 nM), <sup>3</sup>H-R5020 (0.49 to 27 nM), and <sup>3</sup>H-R1881 (0.67 to 18 nM). Nonspecific binding was determined from duplicate assays carried out in the presence of a 100-fold excess of unlabeled hormone. Incubations were carried out for 18 hours at 4° C, after which 0.5 ml of dextra-coated charcoal solution (DCC) was added to each tube and allowed to incubate for 5 minutes before being centrifuged to remove the free hormone. The fraction containing macromolecular bound hormone was decanted into 7 ml of scintillation cocktail (Scintiverse, Fisher) and then counted. Data were analyzed by Scatchard analyses to assess the concentration of specific binding sites in the cytosol and the equilibrium dissociation constants of binding. Cytosol protein concentrations were determined by the Bio-Rad assay, using Coomassie Brilliant Blue G250.11

Competition analyses for the various steroids were performed in the presence of fivefold to 100 fold excess of various radioinert steroids. The macromolecular bound counts were determined as described above. The results were calculated taking into consideration the nonspecific binding and were expressed in terms of relative binding affinity.

#### Results

Scatchard analyses revealed that the 35% ammonium sulfate fraction of the human ovarian cytosol showed a high-affinity binding for testosterone,  $K_d = 3.3 \pm 0.6$ 

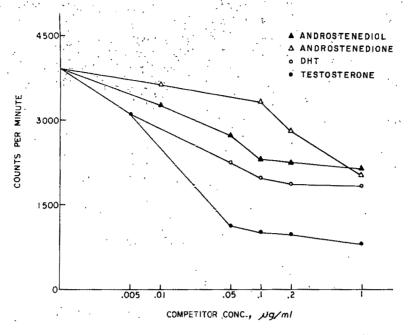


Fig. 2. Competition analysis for <sup>3</sup>H-testosterone by fivefold to 100-fold excess of radioinert testosterone, DHT, androstenedione, and androstenediol. Incubations were performed at 4° C overnight.

nM (n = 3), with a single class of binding sites at a concentration of  $0.36 \pm 0.16$  pmoles/mg of cytosol protein. Fig. 1 demonstrates a typical Scatchard analysis for testosterone. <sup>3</sup>H-DHT (0.4 to 22 nM) was found to bind to the androgen binder,  $K_d = 6.2$  nM, with a single class of binding sites, the concentration of which was 1 pmole/mg of cytosol protein. The K<sub>d</sub> of 2.9 nM for the synthetic androgen, R1881, agrees well-with that found for testosterone. Incubation for 30 minutes at 25° C in the presence of protease (5 mg/ml) caused 91% of the specific binding of testosterone to be abolished. Incubation of the cytosol for 30 minutes at 25° C resulted in a 12% decrease in the specific binding whereas raising the incubation temperature to 45° C (for 30 minutes) resulted in a 53% decrease in specific binding.

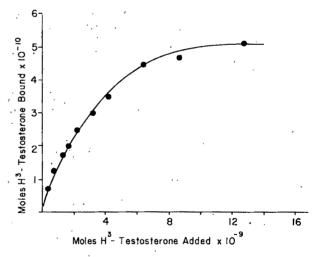
Competition analyses demonstrating the specificity of the high-affinity androgen binder in the ovary are expressed in terms of relative binding affinities (RBA), where

•Concentration of unlabeled testosterone

RBA = 
$$\frac{\text{giving 50\% competition}}{\text{• Concentration of the competitor}} \times 100$$

giving 50% competition

Table I presents the displacement of <sup>3</sup>H-testosterone from the androgen binder by various competitors. This table demonstrates the high specificity of the androgen binder for testosterone. DHT is a considerable competitor, but androstenediol and androstenedione are



**Fig. 3.** Saturation curve for <sup>3</sup>H-testosterone binder in the 35% ammonium sulfate fraction of the human ovary, demonstrating saturability of the binder.

much weaker competitors. R5020 (a synthetic steroid with high affinity for the progesterone receptor) has no displacing ability, which demonstrates the specificity of this binder for androgens. The extremely low relative binding affinity for estradiol precludes any significant binding of estrogens or contamination with serum testosterone-estrogen binding globulin (TEBG). Fig. 2 presents the competition analysis for the testosterone binder by various steroids. Fig. 3 demonstrates the

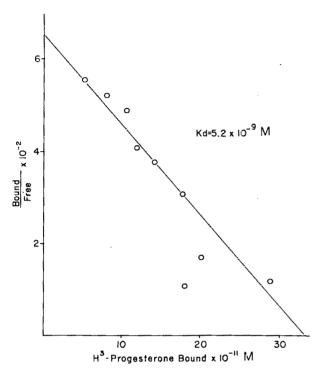


Fig. 4. Scatchard analysis of the progesterone binder in the 35% ammonium sulfate fraction of the human ovary. Incubations (total volume, 0.6 ml) of increasing amounts of <sup>3</sup>H-progesterone (0.4 to 13 nM) in the presence of 100-fold excess of nonlabeled progesterone were performed at 4° C overnight.

saturability of androgen binder. Only 10 nm of testosterine is required to saturate the binder.

Scatchard analysis of the 35% ammonium sulfate fraction of the human ovarian cytosol revealed a highaffinity binder for progesterone,  $K_d = 7.6 \pm 1.8$  nM (n = 6), with a single class of binding sites, the concentration of which was  $0.43 \pm 0.37$  pmole/mg of cytosol protein. Fig. 4 presents a Scatchard analysis for 3Hprogesterone. The average K<sub>d</sub> for the synthetic progestin, R5020, was  $3.6 \pm 3.3$  nM (n = 3), with an average receptor site concentration of  $0.28 \pm 0.22$ pmole/mg of cytosol protein. Table II presents the specificity data for the progesterone binder (shown also for R5020). It does not bind to androgens (testoster-.. one), nor does it bind to cortisol, which also shows that there is no contamination with serum cortisol-binding globulin (CBG). The saturability of the progesterone binder is demonstrated in Fig. 5. As little as 8 nM of progesterone will saturate the binder.

As a control, Scatchard analyses were performed in pregnancy serum for progesterone, testosterone, R1881, and R5020, with and without a 35% ammonium sulfate cut. As expected, only testosterone gave specific binding in the untreated serum, with a  $K_d$  of  $1.2 \times 10^{-8}$ 

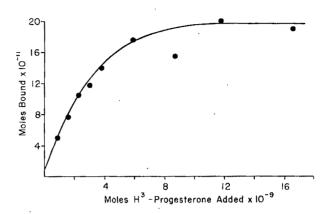


Fig. 5. Saturation curve for <sup>3</sup>H-progesterone binder in the 35% ammonium sulfate fraction of the human ovary, demonstrating saturability of the binder.

**Table II.** Displacement of <sup>3</sup>H-progesterone and <sup>3</sup>H-R5020 from the progesterone binder by competing radioinert steroids (expressed in terms of relative binding affinity

<sup>3</sup> H-steroid	Competing nonlabeled steroid	Relative binding affinity (%)
Progesterone	Progesterone	100
	R5020	100
	Testosterone	<1.0
	Cortisol	0
R5020	R5020	100
•	Progesterone	69.3
	Testosterone	2.0
	Cortisol	0

M. In the serum fractionated with 35% ammonium sulfate, no specific binding was obtained.

#### Comment

The fact that antiandrogens, such as flutamide and cyproterone acetate, reverse the ovarian action of human chorionic gonadotropin on the ovary of the estrogen-stimulated hypophysectomized rat12, 13 encouraged Schreiber and associates3 to search for testosterone receptors in the rat ovary. When they demonstrated the receptor-like, high-affinity, thermolabile, and saturable binder for testosterone, they hypothesized that it might change the level of ovarian androgens in the ovary, thus preventing the estrogeninduced ovarian gain in weight due to proliferation of granulosa cells.14 In a later study,4 they were able to show the selective nuclear uptake of testosterone by granulosa cells and the presence of a nuclear-testosterone protein complex. The conclusion they reached was that an intraovarian control of preantral follicular development exists which is mediated by testosterone.

This report describes a protein in human ovarian cytosol that has the characteristics of an androgen receptor, that is, it has high affinity, a Kd of 3.3 nM, which is similar to the K<sub>d</sub> of the testosterone receptor of the estrogen-stimulated, hypophysectomized rat, described by Schreiber and associates,3 and the Kd of 3 nM reported for the prostatic DHT cytosol receptor. 15 The binder described has specificity for testosterone. DHT is a considerable competitor for the binder, but other androgens, such as androstenediol and androstenedione, are much weaker competitors. The binder is thermolabile, and although it is more heat resistant than the androgen binder found in the rat, it is unlikely that it is an androgen-binding protein. Tindall and associates16 have shown that a temperature of 50° C will decrease the binding to the cytosol receptor in the epididymis and the ventral prostate of the rat; the binding to the androgen-binding protein (ABP) was not influenced by heating to 50° C. By using 35% ammonium sulfate fractionation, we were able to purify the binder and eliminate contamination with serum TEBG.

This report also describes the presence of a receptor-like protein in ovarian cytosol with high affinity for progesterone. It is specific for progesterone and R5020. Cortisol did not displace progesterone or R5020 on this binder, which shows that the ammonium sulfate fractionation removes cortisol-binding globulin, a high-affinity progesterone binder. In tissues in which a high-affinity progesterone binder is found, the presence of an estrogen binder is also usually demonstrated. However we were unable to find a high-affinity binder for estradiol in human ovarian cytosol. It is possible that, because of high levels of endogenous estradiol, such a binder would be present in the nucleus rather than in the cytosol.

It is well documented that receptors in cytosol mediate steroid effects on target tissues. If it is presupposed that the binders demonstrated in this study are receptors, then ovarian function in the human is regulated by both androgens and progesterone. However, neither testosterone nor progesterone has been shown to have an intraovarian effect in the human. Even though there is evidence from studies in the rat to support a target-organ effect for testosterone, none exists for progesterone. In order to study local effects of hormones in the ovary, one must be able to manipulate the hormonal milieu and at the same time observe consequent morphologic and/or functional changes in the tissue. Although these kinds of studies are not easily carried out in human beings, McNatty and associates17 have shown that they are feasible. Insofar as animal models are applicable and/or human studies are possible, experiments should be conducted to determine the implications of the presence of androgen and progesterone receptors in the human ovary to the control of follicular growth and atresia, ovulation, and corpus luteum function.

We wish to thank our colleagues in Baylor-affiliated hospitals for providing us with the surgical material used in this study. We also wish to express our appreciation to Dr. Roy G. Smith, for his comments concerning the manuscript, Dr. Norman Huang, for the illustrations, and Arunee Warren and Christine Harris, for their assistance in preparation of the manuscript.

#### REFERENCES

- 1. Speroff, L., Glass, R. H., and Kase, N. G.: Hormone Biosynthesis, Metabolism and Mechanism of Action in Clinical Gynecologic Endocrinology and Infertility, Baltimore, 1978, The Williams & Wilkins Co., pp. 11-16.
- McNatty, K. P., Makris, A., DeGrazia, C., Osathanondh R., and Ryan, K. J.: The production of progesterone androgens, and estrogens by granulosa cells, thecal tissue. and stromal tissue from human ovaries in vitro, J. Clin. Endocrinol. Metab. 49:687, 1979.
- 3. Schreiber, J. R., Reid, R., and Ross, G. T.: A receptor-like testosterone-binding protein in ovaries from estrogenstimulated hypophysectomized immature female rats, Endocrinology 98:1206, 1976
- 4. Schreiber, J. R., and Ross, G, T.: Further characterization of a rat ovarian testosterone receptor with evidence for nuclear translocation, Endocrinology 99:590, 1976.
- Friberg, L. G., Kullander, S., Persijn, J. P., and Korsten.
   C. B.: On receptors for estrogens (E<sub>2</sub>) and androgens (DHT) in human endometrial carcinoma and ovarian tumors, Acta Obstet. Gynecol. Scand. 57:261, 1978.

- 6. Schreiber, J. R., and Hsueh, A. J. W.: Progesterone "receptor" in rat ovary, Endocrinology 105:915, 1979.
- Jacobs, B. R., and Smith, R. G.: Evidence for a receptorlike protein for progesterone in bovine ovarian cytosol, Endocrinology 106:1276, 1980.
- 8. Christ, J. E. and Lotze, E. C.: The residual ovary syndrome, Obstet. Gynecol. 46:551, 1975.
- Tindall, D. J., Miller, D. A., and Means, A. R.: Characterization of androgen receptor in Sertoli cell-enriched testis, Endocrinology 101:13, 1977.
- 10. Scatchard, G.: The attractions of proteins for small molecules and ions, Ann. N. Y. Acad. Sci. 51:660, 1949.
- 11. Sedmak, J. J., and Grossberg, S. E.: A rapid, sensitive and versatile assay for protein using Coomassie Brilliant Blue G250, Anal. Biochem. 79:544, 1977.
- 12. Neri, R., Florance, K., Koziol, P., and Van Cleave, S.: A biological profile of a nonsteroidal antiandrogen SCH 13521 (4'-nitro-3'-trifluromethylisobutyranilide), Endocrinology 91:427, 1972.
- 13. Liao, S., Howell, D. K., and Chang, T-M.: Action of a nonsteroidal antiandrogen, flutamide, on the receptor

- binding and nuclear retention of  $5\alpha$ -dihydrotesterone in rat ventral prostate, Endocrinology **94:**1205, 1974.
- Louvet, J. P., Harman, S. M., Schreiber, J. R., and Ross, G. T.: Evidence for role of androgens in follicular maturation, Endocrinology 97:366, 1975.
- uration, Endocrinology 97:366, 1975.
  15. Pita, J. C., Jr., Lippman, M. E., Thompson, E. B., and Loriaux, D. L.: Interaction of spironolactone and digitalis with the 5α-dihydrotestosterone (DHT) receptor of rat ventral prostate, Endocrinology 97:1521, 1975.
- Tindall, D. J., Hansson, V., McLean, W. S., Ritzen, E. M., Nayfeh, S. N., and French, F. S.: Androgen-binding pro-
- teins in rat epididymis: Properties of a cytoplasmic receptor for androgen similar to the androgen receptor in ventral prostate and different from androgen-binding protein (ABP), Mol. Cell. Endocrinol. 3:83, 1975.
- 17. McNatty, K. P., Smith, D. M., Makris, A., Osathanondh, R., and Ryan, K. J.: The microenvironment of the human antral follicle: Interrelationships among the steroid levels in antral fluid, the population of granulosa cells, and the status of the oocyte in vivo and in vitro, J. Clin. Endocrinol. Metab. 49:851, 1979.

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following written statement, signed by one author: "The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C. V. Mosby Company in the event the work is published. The undersigned author warrants that the article is original, is not under consideration by another journal, and has not been previously published. I sign for and accept responsibility for releasing this material on behalf of any and all co-authors." Authors will be consulted, when possible, regarding republication of their material.

# The use of medroxyprogesterone acetate for relief of climacteric symptoms

JOHN C. MORRISON, M.D.

DAN C. MARTIN, M.D.

RICHARD A. BLAIR, M.D.

GARLAND D. ANDERSON, M.D.

BRADFORD W. KINCHELOE, M.D.

G. WILLIAM BATES, M.D.

JAMES W. HENDRIX, M.D.

MICHEL E. RIVLIN, M.D.

EVELYN K. FORMAN

MAUREEN G. PROPST, M.N., R.N.

ROBERT NEEDHAM, M.S.

Memphis, Tennessee, Jackson, Mississibpi, and Kalamazoo. Michigan

Climacteric symptoms in the menopausal woman are perplexing to the physician. Recent literature concerning the relationship of estrogen to carcinogenesis has caused many women to discontinue this medication; thus, there is a need for an alternative therapy for the relief of these symptoms. The drug medroxyprogesterone acetate (Depo-Provera) was assessed in a double-blind, randomized, placebo-controlled study involving 48 subjects. Only one of the placebo-treated patients claimed any relief from climacteric symptoms while only two of the patients who received the study drug noted little or no relief (P < 0.0001). Relief from climacteric symptoms began at 4 to 7 days after entry into the study and extended for 8 to 20 weeks. The only side effects were withdrawal bleeding and a slight, transient weight gain. Depo-Provera appears to  $\exists$ e a reliable substitute for estrogen in the treatment of climacteric symptoms. Further investigations with this medication seem indicated. (AM. J. OBSTET. GYNECOL. 138:99, 1980.)

DURING THE TRANSITION between the menstrual and postmenstrual years, commonly known as the perimenopausal period, there is a gradual diminution in the amount of estrogen produced by the ovaries while the amount of pituitary gonadotropins secreted by the adenohypophysis is increased in a compensatory effort to sustain failing ovarian function. This change in hormonal milieu of the postmenopausal woman as

From the Department of Obstetrics and Cynecology, University of Tennessee Center for the Health Sciences, Memphis; the Department of Obstetrics and Gynecology, Unniversity of Mississippi Medical Center, Jackson; and The Upjohn Company, Kalamazoo.

Received for publication January 3, 1980.

Revised April 1, 1980.

Accepted April 8, 1980.

Reprint requests: John C. Morrison, M.D., University of Mississippi Medical Center, Jackson, Mississippi 39216.

well as the castrated woman may be accompanied by various symptomatic and clinically significant changes. Vasomotor symptoms such as "hot flashes" are common in this group of women. These vasomotor symptoms vary in their severity from slightly bothersome to incapacitating and may occur in up to 30% to 50% of women at risk.<sup>2</sup> Other symptoms such as vaginal atrophy, insomnia, nervousness, and night sweats also are frequent complaints. Osteoporosis, related to estrogen deprivation, may result in hip fracture, which is one of the most common causes of death and disability in the geriatric age group.<sup>3</sup> All of these symptoms are becoming more frequent since more women are surviving for a longer period of time. Therefore, the relief of these climacteric symptoms appears important.

Many women affected with climacteric symptoms have derived significant benefit from hormonal replacement with natural or synthetic estrogens. In most

Table I. Demographic data

	DMPA				
	150 :ng	100 mg	50 mg	Placebo	
Age*	43.0 ± 9.9	$44.9 \pm 7.1$	$39.8 \pm 12.6$	$53.2 \pm 6.6$	
No. of white patients/No. of black patients	9/3	9/3	-8/4	8/4	
Prior hysterectomy*	11/12	8/12	<sup>3</sup> 9/12	3/12	
Parity	$3.2 \pm 2.3$	$1.8 \pm 1.5$	$1.7 \pm 1.6$	$2.9 \pm 1.7$	
Atrophic maturation index†	10	. 11.	(11	11	

<sup>\*</sup>Significant at P < 0.0008.

**Table II.** Patient discontinuance in DMPA study for treatment failure

	DMPA			
	150 mg	100 mg	50 mg	Placebo
Discontinuance due to treatment failure	0	0	2	9

cases, this medication will reduce the severity of hot flashes and decrease the rate at which they occur, as well as having a positive effect on the other symptoms. However, there are many subjects with menopausal symptoms in whom estrogen compounds are contraindicated. These relative contraindications include a history of adenocarcinoma of the uterus or breast, thrombophlebitis, hypertension, liver disease, and diabetes.<sup>5</sup> In addition, there are other subjects who are symptomatic but in whom estrogen, even in small amounts, causes more undesirable symptoms such as mastodynia, worsening of fibrocystic disease, breakthrough bleeding, gastrointestinal difficulties, and growth of leiomyomas. Moreover, recent literature, although not substantiated, has indicated a possible association between growth of certain forms of hormonally responsive carcinomas and the use of estrogens.6 Finally, some women do not show a diminution of vasomotor symptoms even with large doses of estrogens.4

These exclusion categories appear to comprise a large number of women with climacteric symptoms in whom estrogen therapy is not tenable. For these subjects the alternatives to estrogen are tranquilizers, mood elevators, anticholinergic agents, diuretics, and androgens, methods which have enjoyed limited to variable success. Because oncologists had noted some relief of "hot flashes" in postmenopausal women treated with medroxyprogesterone acetate (Depo-Provera) for metastatic cancer, the drug appeared to offer some promise in treatment of normal subjects suffering from vasomotor symptoms.<sup>7</sup>

This study was designed to assess the effectiveness of

Depo-Provera (DMPA) in alleviating the intensity and number of "hot flashes" in perimenopausal and postmenopausal women as well as those surgically castrated. Provisions were taken to assess the lowest possible effective dosage of DMPA since previous studies demonstrated the drug to be complicated by certain side effects at the "routine" dose of 150 mg/month.<sup>7</sup> It was hoped that those subjects in whom estrogens are contraindicated or intolerable might be afforded relief from climacteric symptoms by this drug.

#### Material and methods

This study was a randomized, double-blind, placebo-controlled investigation of three dosage schedules (50, 100, and 150 mg) for DMPA. Patients entering the study were menopausal or perimenopausal (naturally or surgically). All had a significant number of hot flashes and night sweats (more than one per day). None of the subjects had evidence of malignancy or contraindication to hormonal therapy. They were judged as reliable in keeping records of subjective symptoms and were able to return at regular intervals for evaluation. Patients were further willing to have the medicine injected intramuscularly, were agreeable to having blood drawn for laboratory analysis, and understood they might receive a placebo.

The primary measurable endpoint of the study was the hot flash. As a method of quantitation, these patients had at least one hot flash daily and had been experiencing this symptom regularly for at least 4 weeks prior to starting the program. Response was graded by history as: (1) minimal response (25% reduction in frequency), (2) fair response (50% reduction), (3) good response (75% reduction), or (4) excellent response (total elimination of hot flashes). The frequency of vasomotor symptoms was kept on a "hot flash calendar" on which data were recorded daily. The incidence and severity of vaginal bleeding were similarly recorded.

Some subjects had been taking estrogen compounds for relief of vasomotor symptoms in the past, but not

<sup>†</sup>Less than 20% superficial cells (indicating lesser estrogen effect).

within 4 weeks of entering the study. A maturation index was obtained in each patient to confirm the absence of normal amounts of estrogen. Patients were excluded from the study if they had hepatitis, active renal disease, hypertension, history of thromboembolic disease, regular menstrual function, female genital cancer, positive Papanicolaou smear, or undiagnosed pelvic pathologic condition.

After assessment, 48 eligible candidates entered the study, signed informed consent forms, and underwent a physical examination including breast examination, bimanual pelvic assessment, Papanicólaou smeár, and maturation index. Pertinent laboratory data obtained at the initial visit included a complete blood count, urinalysis, and determination of serum glutamic oxaloacetic transaminase, alkaline phosphatase, bilirubin, blood urea nitrogen, and glucose. After a 2-week observation period to establish a baseline, each participant had one injection of either DMPA or placebo. She was then evaluated historically at 2, 4, 6, 8, 10, and 12 weeks after injection. Physical and laboratory examination as outlined above was also performed at 4 and 12 weeks after medication.

#### Results

Table I shows that the age, parity, and incidence of hysterectomy in the treatment group are different from those of the placebo group. Also a significant number of women in the group receiving DMPA had had prior hysterectomy, many at an early age, which perhaps accounts for the low age of the DMPA patients. These differences were significant at the P < 0.0008 level. Other assessment criteria, such as the initial number of hot flashes, the onset and length of symptomatology, race, gravidity, parity, age of menarche, prior gynecologic symptoms, associated medication or symptomatology, and the incidence of prior estrogen therapy were not significantly different in each group. Likewise, the laboratory assessment revealed only occasional aberrations from normal in the random blood glucose and liver function studies and these were equally distributed between the two groups. Finally, the maturation index in most patients indicated an atrophic or nonestrogenic vaginal smear.

There were significant differences between the treatment and placebo groups when the patient dropout rate, subjective improvement, and satisfaction with therapy as well as the diminution in number of hor flashes and night sweats were considered. Table II shows that among the 24 patients in the 100 and 150 mg DMPA groups no patient discontinued the study b∈cause of treatment failure. In those receiving 50 mg cf the parent compound, two patients discontinued the

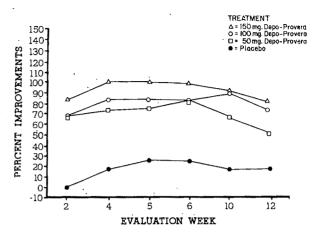


Fig. 1. Percent improvement in subjective symptoms of patients receiving Depo-Provera or placebo.

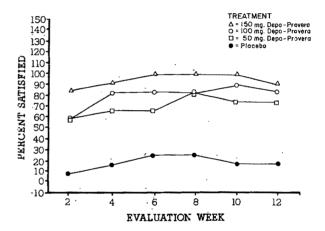


Fig. 2. Percent of patients satisfied with treatment regimen (Depo-Provera or placebo).

study at 6 and 8 weeks respectively. However, 75% of the placebo group dropped out of the study between 6 and 10 weeks (average 6.5 weeks). Therefore, only three of the 12 patients who received placebo completed the entire 12-week study period, whereas only two of the 36 patients receiving DMPA dropped out because of treatment failure. The difference between these figures is highly statistically significant (P < 0.0002).

Improvement in the patient's perception of relief of symptoms is shown in Fig. 1. These data demonstrate that in general the placebo patients demonstrated an improvement of 15% to 20% in their symptomatology during the course of therapy. This placebo effect, however, was extremely variable among patients at each assessment period and all patients in this group reported feeling worse compared to their initial evaluation on at least one follow-up visit. When the placebo patients are compared to those receiving DMPA there is a wide difference, with the treatment group showing 75% to 100% relief of symptoms between the second ...

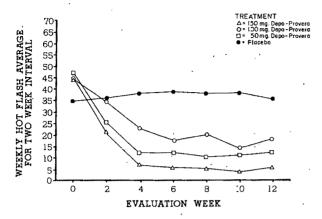


Fig. 3. Relationship of treatment to mean number of hot flashes/night sweats per week.

Table III. Side effects in DMPA study patients\*

Side effect	150 mg	100.mg	50 mg	Placebo
Emotional lability	2	1	1	3
Weight gain	1	1	1	1
Breast tenderness	1	1	0	Ó
Menorrhagia	0	1	1	1
Acne	1	1	ó	0
Depression	0	1	1	3

<sup>\*</sup>After initial 2 weeks.

week and the fourth week after treatment was begun. In general, there was a stratification at each bimonthly evaluation period indicating greater improvement with all doses of DMPA compared to placebo. The differences between the three levels of active medication did not show the expected dose-response curve. There was, however, a trend toward a reduction in symptomatic relief in the tenth and twelfth weeks in those receiving 50 mg of DMPA compared to the other two dosage regimens of active medication.

Fig. 2 displays the percent of patients satisfied with the treatment. Those in the placebo group indicated a slight improvement over symptomatology on the initial visit, but this response was variable. The difference in satisfaction with treatment was evident when any or all of the DMPA group were compared to the placebo. There appeared to be stratification in satisfaction based on the amount of DMPA administered among the three groups of patients receiving the parent compound, however, this trend was not statistically significant.

The data in Fig. 3 demonstrate the change in mean number of hot flashes and night sweats at each 2-week interval; the weekly average of these vasomotor symptoms depicts changes in each category. Those patients

in the placebo group appeared continually to have 35 or 40 hot flashes per week throughout the entire 12-week evalvation period. After injection all patients receiving the DMPA evidenced a 25% to 45% reduction in the frequency of these vasomotor symptoms; this result was significantly different from that of the placebo group. The reduction continued through the fourth week and then plateaued between 5% and 50% of the original level for the remainder of the study. Although there appear to be differences in response among the patients receiving the various dosages of DMPA, the results are not statistically significant for this limited sample.

Table III shows the side effects occurring in these patients. Only three patients (two in the treatment group and one in the placebo group) had irregular bleeding. None of these required surgical intervention. Only one patient in each group had a slight weight gain. In general, the symptoms of emotional lability and depression, which were present initially, resolved in most instances by the third week of treatment. The physical examinations and laboratory data at 4 and 12 weeks, respectively, were summarized and compared to the initial data. No remarkable changes occurred in the variables as they were compared to the treatment schedule or to the data obtained from the initial visit.

#### Comment

The vasomotor symptoms found in women with failing ovarian function is not clearly related to any one factor. The most obvious cause of these hot flashes can be correlated to the diminishing amount of estrogen found during this period. Support for this theory is found in the data which show that hot flashes have been relieved by the administration of estrogens in women with these symptoms.4 However, this may not be the only mechanism for the development of these vasomotor signs since hot flashes are also observed during pregnancy, when the estrogen levels are actually higher than in the nonpregnant normal woman.8 In addition, many postmenopausal women who have very low estrogen levels never develop these symptoms.4 Moreover, other subjects with very low estrogen levels, such as normal men, prepubertal female subjects, and subjects with gonadal dysgenesis or postpill amenorrhea rarely have hot flashes.9

Another theory concerning the etiology of the hot flashes is that they may be attributed to the elevated gonadotropin levels which occur during the postmenopausal period. This theory also is far from complete since conditions with elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH),

such as constitutional isosexual precocity, and Klinefelter's syndrome may not evidence hot flashes as a manifestation unless they are sensitized to estrogen. In addition, the medication Danazol, a potent antigonadotropin substance which markedly lowers the LH/FSH level, has been tested in postmenopausal women and does not affect the severity or incidence of hot flashes.12 Other factors such as vasoactive substances, peripheral conversion of hormones, changes in remote, endocrinologically active areas affected by a low estrogen/high gonadotropin ratio, and unknown factors may be involved in the vasomotor instability causing these symptoms.4, 13

Bullock and colleagues7 have shown that DMPA is efficacious in the reduction of the severity and number of vasomotor symptoms in the postmenopausal woman. The mechanism by which this drug inhibits the hot flashes is unclear. There is disagreement as to the effect of the medication on gonadotropin levels. Some demonstrate a complete and even suppression of gonadotropin,12 while others showed variable effects.14, 15 LH appears to be involved in the genesis of climacteric symptoms and DMPA seems to affect the gonadotropin production or its end-organ effect. 10

Clinically, Bullock and co-workers found that the administration of DMPA (150 mg intramuscularly) brought prompt and complete relief of hot flashes in 51 of 57 (89.5%) patients so treated. This was compared to three of 12 patients (25%) who obtained relief of their symptoms by placebo. The side effects noted in approximately 10% of the patients were limited to irregular spotting, fluid retention, and depression. Others9, 10 have also found this drug effective for relief of climacteric symptoms.

Seymour and Powell<sup>16</sup> found that the irregular bleeding could be controlled by giving small doses of estrogen for the first 7 days of each month. There is also much evidence that the administration of this drug relieves hot flashes in castrated women with metastatic cancer.6

The data in the current study confirm that this drug, regardless of its method of action, appears to reduce the number of climacteric symptoms in perimenopausal and postmenopausal women. Previous studies have addressed the question in aged women and in those with cancer. There is good evidence from this study that the drug works equally well in young women who have surgically lost ovarian function. The difference in age, in this study, is probably related to the preponderance of patients having prior hysterectomies in the treated group. It is logical to assume that if a woman is postmenopausal at an early age, the deciding

factor was probably surgical intervention. Although it is unlikely that the age or prior hysterectomy difference in each group had a material bearing on the results of the study with reference to climacteric symptoms, the weighted age difference in the DMPA groups remains unexplained.

We had hoped to show a difference in side effects or efficacy at various dosage levels of DMPA. However, since the vast majority of patients had experienced prior hysterectomy, the incidence of irregular bleeding could not be tabulated. In contrast to the studies by Bullock and colleagues2, 7 we did not find a high incidence of abnormal bleeding. There were slightly more patients in the placebo group who experienced transient depression, emotional lability, and weight gain, but this was not statistically significant. Breast tenderness, edema, nausea, and vaginal dryness occurred occasionally and were evenly distributed in each group. It must be remembered that symptoms such as vaginal atrophy or osteoporesis will not be affected by DMPA.

There were apparent differences within the treatment group in the perception of how the patient felt and her satisfaction with treatment. At the 8-, 10-, and 12-week visits more patients were satisfied and felt better if they had received 150 or 100 mg of DMPA as compared to the 50 mg dose. This was only a trend, however, and no statistically significant difference was present. Therefore, no comparison can be made as to side effects or efficacy among the three dosage levels of DMPA.

This study has shown that DMPA is efficacious in decreasing the number of hot flashes, in providing a subjective increase in sense of well-being, and in providing patient satisfaction with the treatment regimen. This therapy is also effective in the young castrated woman, whereas previous investigations have shown effectiveness only in aged women with and without cancer. Therefore, it appears to be a logical choice in women severely affected by climacteric symptoms who are physiologically or psychologically intolerant of estrogen compounds or who do not receive relief from hormonal therapy. This study does not answer the question of the smallest effective dose of DMPA, although a trend toward relief of symptoms for a longer period of time with higher doses of DMPA was found. It would appear that perhaps a large, multicenter study might better demonstrate the efficacy at various dosage levels of DMPA and incidence of side effects in women with climacteric symptoms. Nevertheless, the drug does appear to be effective for relief of climacteric symptoms and no unusual side effects have been noted in this or other studies. Further work seems indicated.

#### REFERENCES

- Chan, L., and O'Malley, B. W.: Mechanism of action of sex steroid hormones, N. Engl. J. Med. 294:1430, 1976.
- 2. Bullock, J. L.: Progestin therapy: An adjunct in managing the menopause, Contemp. Ob/Gyn 6:13, 1975.
- Gordon, G. S., and Genant, H. K.: Postmenopausal osteoporesis is a preventable disease, Contemp. Ob/Gyn 11:47, 1978.
- 4. Bohler, C. S. S., and Greenblatt, R. B.: The pathophysiology of the hot flash, in Greenblatt, R. B.. Mahesh, V. B., and McDonough, P. G., editors: The Menopausal Syndrome, New York, 1974, MEDCOM Press, pp. 29-37.
- drome, New York, 1974, MEDCOM Press, pp. 29-37.

  5. Kistner, R. W., editor: The Use of Progestins, Year Book Medical Publishers, Inc., Chicago, 1969, pp. 70-71.
- Hertz, R.: The estrogen-cancer hypothesis, Cancer (Suppl.) 38:534, 1976.
- Bullock, J. L., Massey, P. M., and Gambrell, R. D.: Use of medroxyprogesterone acetate to prevent menopausal symptoms, Obstet. Gynecol. 46:2, 1975.
- 8. Siiteri, P. K., and McDonald, P. C.: Placental estrogen biosynthesis during human pregnancy, J. Clin. Endocrinol. Metab. 26:751, 1966.
- 9. Morrison, J. C., Givens, J. R., and Summit, R. A.: Gonadal dysgenesis, Med. Bull. 32:7, 1975.

- Meldrum, D. R., Tataryn, I. V., Frumar, A. M., and Judd, H. L.: Hot flashes and LH levels, Presented at the Annual Meeting of the Endocrine Society, 1978.
- 11. Kupperman, H. S., and Epstein, J. A.: Medroxyprogesterone acetate in the treatment of constitutional sexual precocity, J. Clin. Endocrinol. Metab. 22:456, 1962.
- Mishell, D. R.: Effect of 6-methyl-17hydroxyprogesterone on urinary excretion of luteinizing hormone, Am. J. Obstet. Gynecol. 99:86, 1967.
- Miyake, T.: Inhibitor effects of various steroids on gonadotropin hypertension in parabiotic mice, Endocrinology 69:534, 1961.
- 14. Goldzieher, J. W., Kleber, J. W., Moses, L. E., et al.: A cross-sectional study of plasma FSH and LH levels in women using sequential, combination or injectable steroid over long periods of time, Contraception 2:225, 1970.
- Gaspard, U., Franchimont, P., Beco, G., et al.: The action of medroxyprogesterone on the level of serum gonadotropin in women with normal menstrual cycles, C. R. Soc. Biol. (Paris) 163:2456, 1969.
- Seymour, R. J., and Powell, L. C.: Depo-medroxyprogesterone acetate: A contraceptive, Obstet. Gynecol. 36:589, 1970.

### CURRENT DEVELOPMENTS

# The obstetrician's opportunity: Translating "breast is best" from theory to practice

BEVERLY WINIKOFF, M.D., M.P.H. EDWARD C. BAER, B.A.

New York, New York

The superiority of breast-feeding to artificial feeding of infants has been well established for nutritional, biochemical, antiinfective, psychological, economic, and contraceptive reasons. The promotion of breast-feeding should, therefore, be a high-priority concern of health workers. Both provision of information and support to expectant mothers and changes in hospital routines in the perinatal period have been shown capable of dramatically increasing the incidence and duration of breast-feeding in populations studied. Mcreover, these interventions are quite specific, effective, manageable, and affordable. Obstetricians have a special responsibility and capacity to promote breast-feeding given their contact with women throughour pregnancy and their influence on hospital birth routines. A greater commitment on the part of obstetricians to promote breast-feeding could accelerate and extend the current shift back to breast-feeding, to the benefit of mothers and their babies in all socioeconomic groups. (Am. J. Obstet. Gymecol. 138:105, 1980.)

EACH YEAR, scientific evidence provides increasing justification for promoting breast-feeding. While the protective effects of breast-feeding against common infections are especially important in unsanitary environments, mounting clinical and epidemiologic evidence demonstrates distinct advantages, even in modern industrialized societies. However, theoretical knowledge of the superiority of breast-feeding has seldom been translated into a commitment to promote it in the community.

Re-examination of attempts to promote breast-feeding demonstrates, nevertheless, that enlightened medical practice can substantially increase the prevalence and length of successful lactation. The common perception that trends away from breast-feeding are an

From The Population Council.

Reprint requests: Beverly Winihoff, M.D., The Population Council, One Dag Hammarshjold Plaza, New York, New York 10017.

inevitable part of "modernization" and are difficult to reverse does not seem to be accurate. In fact, there appears to be a series of specific, manageable steps that can increase markedly the incidence and duration of breast-feeding, and, as a bonus, they are not costly to implement. It seems that there are no special secrets to promotion of breast-feeding; what a rational person would think might work does, in fact, work. (See Table I.)

Finally, analysis of the key points for intervention demonstrates that most are closely linked to obstetric practice and attitudes for several reasons. First, in the United States, obstetricians bear central responsibility for delivering prenatal care directly to patients, for setting medical standards for maternity services, and for providing public information on pregnancy and childbirth. Second, obstetricians generally are charged with supervising and monitoring the performance of labor and delivery services in hospitals. Third, obstetric attitudes and practices act on the mother throughout

Table I. Summary of selected intervention program effects on incidence and duration of breast-feeding

	•				
Source	Place	Type of intervention	Sample size	Time of measurement	
nformation and support: Brimblecombe and Cullen <sup>21</sup> (1977)	Exeter, England	Education of midwives and health visitors on consul- tant unit (L)	562	Hospital discharge	
Burne <sup>55</sup> (1976)	Oxford, England	Continuity of care by stable, familiar health	73	6 weeks post partum	
Coles and Valman <sup>92</sup> (1976)	Harrow, England	team (L) Hospital-based education	±1,300	Hospital discharge	
Creery <sup>33</sup> (1973)	Cheltenham, England	program (L) Education of health pro- fessionals (L)	4,950	Hospital discharge	
De Chateau et al. <sup>67</sup> (1977)	Umea, Sweden	Education of fathers (P)	23	Duration	
Halpern et al. <sup>25</sup> (1972)	Dallas, Texas	Positive attitudes of pediatricians (C)	4,753	*	
Kirk <sup>93</sup> (1978)	Edinburgh, Scotland	Education by doctors and nurses (L)	278	Initiation 1 mo post partum 4 mo post partum	
Meyer <sup>13</sup> (1968)	U.S. hospitals	Hospital programs to pro- mote breast-feeding (unspecified (C)	2,951 hospitals	Hospital discharge	
Rawlins <sup>94</sup> (1978)	Indiana	Obstetric counseling and group support (L)	*	Hospital discharge 5 mo post partum	
Sjölin <sup>95</sup> (1976)	Uppsala, Sweden	Mass media education (L)	*	1 mo post partum 2 mo post partum 4 mo post partum 6 mo post partum	-
Sloper et al. <sup>29</sup> (1977)	Oxford, England	Education of midwives and health visitors (L)	256	Hospital discharge 5 mo post partum	
Sloper et al. <sup>30</sup> (1975)	Oxford, England	Education of midwives (L)	435	Hospital discharge	
Smart and Bam- ford <sup>54</sup> (1976)	Manchester, England	Education of hospital staff (L)	1,448	Hospital discharge	•
Waller <sup>45</sup> (1946)	Woolwich, England	Daily expression of colos- trum (P)	200	*	
Changes in hospital routines: Bjerre and Eke- lund <sup>73</sup> (1970)	Malmö, Sweden	Rooming-in (P)	3,214	Hospital discharge	•
Clavano <sup>76</sup> (1978)	Baguio, Philippines	Rooming-in, no supple- mentary food (L)	10,000	* .	
De Chateau <sup>65</sup> (1976)	Umea, Sweden	Skin-to-skin contact and immediate suckling after birth (P)	40	· 3 mo post partum	
De Chateau et al. <sup>67</sup> (1977)	Umea, Sweden	No routine weighings and no supplementary food (P)	390	Duration	•
		Skin-to-skin contact and immediate suckling after birth (P)	42	Duration	
Jackson et al. <sup>71</sup> (1956)	New Haven, Connecti- cut	Rooming-in (P)	282	Duration •	
Johnson <sup>66</sup> (1976)	Seattle, Washington	Immediate suckling after birth (P)	12	2 mo post partum	•
Klaus and Ken- nell <sup>10</sup> (1976)	Guatemala City, Guatemala (Social Security Hospital)	Immediate suckling after birth (P)	40	6 mo post partum 12 mo post partum	

C = Cross-sectional. L = Longitudinal. P = Prospective controlled.

<sup>\*</sup>Not given.

% Breast-feeding or duration of	% Breast-feeding or duration of	Net increase in %
breast-feeding	breast-feeding - after inter-	breast-feeding
before inter- vention (or in	vention (or in	or duration
control group)	control group)	of breast-feeding
42.5%	51.0%	8.5%
32.0%	69.0%	37.0%
,		\$
54.7%	69.4%	14.7%
45.0%	64.0%	19.0%
75 days (fathers not informed)	135 days (fathers informed)	60 days
14.5% (pediatri-	29.1% (pediatri-	14.6%
cians indiffer-	cians not indif-	121070
ent about	ferent)	
breast-feeding)	, , , , , , , , , , , , , , , , , , , ,	
43.6%	68.5%	24.9%
26.9%	43.5%	37.0%
10.3%	37.0%	26.7%
18.0% (overall	34.8% (for hos-	16.8%
rate)	pital with breast-feeding	
99.00	program)	99.00/
33.0%	65.0%	32.0% 37.0%
15.0% 39.5%	52.0% 78.8%	49.3%
22.1%	69.0%	45.9%
6.0%	39.4%	33.4%
1.0%	15.4%	14.4%
37.0%	52.0%	15.0%
23.0%	43.0%	20.0%
14.0%	37.0%	23.0%
		• • • • • • • • • • • • • • • • • • • •
37.0%	44.0%	7.0%
56.0%	83.0%	27.0%
• ## 000	93.0%	. 17.00
76.0%		17.0%
26.4%	87.3%	60.9%
26.0%	58.0%	32.0%
42 days	95 days	53 days
108 days	175 days	67 days
1.77 mo •	3.14 mo	1.37 mo
16.6%	100.0%	83.4%
16 70	* EQ 00"	
16.7%	52.9%	
0.0%	29.4%	

pregnancy, labor, and delivery and have a marked influence on initial infant feeding choices. Despite the appealing logic of assuming that the neonate is the pediatrician's patient, obstetricians simply cannot divest themselves of the responsibility for promoting appropriate patterns of infant feeding. The evidence suggests that obstetric specialists have, along with unique responsibilities, unmatched opportunities and abilities to perform this service well.

#### Why promote breast-feeding?

Significant nutritional, immunologic, biochemical, antiallergenic, psychological, contraceptive, and economic advantages of breast-feeding have been well documented in the scientific literature.4-8 A wide range of clinical experiments has established the value of breast-feeding in preventing gastroenteritis, respiratory tract infections, necrotizing enterocolitis, otitis media, shigella infections, hypocalcemia, hypernatremia, obesity, cow's milk allergy, asthma, and a variety of other diseases. The psychological implications of successful mother-child bonding, a process enhanced by breast-feeding, are only now beginning to be understood and appear crucial to harmonious early development.10, 11 Because of this extensive documentation, endorsements of the crucial importance of breastfeeding have come from the World Health Organization, the International Pediatrics Association, the British Department of Health and Social Security, and the American Academy of Pediatrics, which recently stated: "Ideally, breast milk should be practically the only source of nutrients for the first four to six months for most infants." ·

The history of breast-feeding patterns in industrialized countries has shown two major trends since the early twentieth century. Breast-feeding in the United States and Western Europe began to decline dramatically in the 1930s and 1940s, this trend lasting through the 1960s.12 In 1966, only 18% of mothers in the United States were exclusively breast-feeding their babies upon hospital discharge.13 In the last several years, however, breast-feeding in the industrialized countries has enjoyed a new surge of popularity-14 Unlike the situation in most developing countries, where the rich breast-feed the least, in industrialized nations middle- and upper-class mothers breast-feed more and longer than the poor. It may be that, as with the adoption of artificial feeding earlier in this century, the poor will follow the rich classes back to breast-feeding in the future. However, the possibility that the shift back to breast-feeding may eventually include the poor is no justification for failing to hasten the process, especially since breast-feeding among low-income groups in the ... United States continues to be extremely rare. 15

Table I-Cont'd

			1	
			,	,
Source	Place	Type of intervention	Sample size	Time of measurement
Changes in hospital routin	es—Cont'd:			
McBryde <sup>74</sup> (1951)	Durham, North Caro- lina	Rooming-in (L)	2,067	Hospital discharge
Salariya et al. <sup>68</sup> (1978)	Dundee, England	Early initiation and in- creased frequency of breast-feeding (P)	. 111	Duration
Sosa et al. <sup>64</sup> (1976)	Guatemala City, Guate- mala (Roosevelt Hos- pital)	Immediate suckling after birth (P)	68	Duration
	Guatemala City, Guate- mala (Social Security Hospital)	Immed ate suckling after birth (P)	40	Duration
Sousa et al. <sup>75</sup> (1974)	Pelotas, Brazil	Immediate suckling and rooming-in (P)	200	2 mo post partum
Combined programs:			•	•
Jepson et al. <sup>90</sup> (1976)	Sheffield, England	Education and changes in hospital routines (L)	11,658	Intention to breast- feed
Švejcar <sup>96</sup> (1977)	Prague, Czechoslovakia	Education of nursing staff and demand feeding and rooming-in (L)	*	l mo post partum Hospital discharge
Wong <sup>91</sup> (1975)	Singapore	Support of breast-feeding by hospital staff and no supplementary feeding (P)	*	Initiation

#### Traditional versus modern societies: The need for planned interventions

Lactation is almost always successful in traditional societies in contrast with the high rates of lactation failure often reported in industrialized societies.4, 16 In traditional societies, no alternative to breast-feeding is perceived or practiced. Pressures to bottle-feed (e.g., commercial advertising of milk substitutes, misguided advice of medical practitioners, supplantation of the breast's nurturing functions by its erotic role) are conspicuously absent. In short, breast-feeding is viewed as a routine, socially acceptable, necessary activity expected of every mother of every new baby. In Western industrial societies, the development of nutritionally acceptable artificial substitutes has meant that breastfeeding is no longer essential for infant survival. The high value placed on "scientific feeding," the indifference or ignorance of the health professions, the desire of some women for time away from infant care, and the aggressive promotion of infant formula combine to demote the importance of breast-feeding. In fact, breast-feeding has been explicitly rejected as embarrassing, crude, and primitive.17. 18

The lack of emotional and social support for breast-feeding in industrialized culture is held by many to be a key determinant of breast-feeding failure.<sup>19, 20</sup> Marked

declines in breast-feeding have been observed among immigrants to Western cultures, 18 reflecting the accessibility of substitutes and the generally low esteem for breast-feeding in modern society. In modern, Westernized culture, with reinforcement for breast-feeding generally lacking in the social system, it falls to health care institutions to provide information as well as surrogates for the supportive atmosphere of traditional societies. Breast-feeding promotion programs in industrialized countries operate within a context in which bottle-feeding is treated as an appropriate infant feeding method and where infant formula is made available to all mothers on the shelf of the local store as well as distributed free to the hospital nursery. Nevertheless, even under conditions typical of advanced societies, focused institutional programs show significant measures of success in the promotion of breast-feeding.

#### Factors affecting breast-feeding

Personal and social correlates of breast-feeding. The most significant correlate of successful breast-feeding is social class. Virtually every study of breast-feeding patterns in Western nations in the last 20 years reveals a clear positive correlation between successful breast-feeding and higher social class. 14. 21-30 Factors such as education, which are linked with social class, are

, o b	Breast-feeding or duration of oreast-feeding before inter- cention (or in ontrol group)	% Breast-feeding or duration of breast-feeding after inter- vention (or in control group)	Net increase in % breast-feeding or duration of breast-feeding
	35.0%	58.5%	23.5%
	77 days	182 days	105 days
	109 days	159 days	50 days
	104 days	196 days	92 days
	27.0%	77.0%	50.0%
	36.0%	59.0%	23.0%
	21.8% 67.0%	27.7% 81.0%	5.9% 14.0%
	47.0%	72.0%	25.0%

similarly correlated.<sup>14, 22</sup> For other factors, such as parity, maternal age, marital status, how the mother herself was fed as an infant, place of residence, place of delivery, difficulty of delivery, sex of infant, ethnic group, etc., the evidence is at best suggestive and at worst contradictory.

A composite profile of women most likely to breast-feed identifies those who are from middle and upper classes, well educated, older than 25 years, married, and were themselves breast-fed. Parity is a confusing factor: Some studies show no independent influence,<sup>30, 21</sup> while others suggest that primiparous women are more likely to initiate breast-feeding<sup>23</sup> but also are more likely to give it up.<sup>26</sup> For multiparous women, a strong correlation exists between how previous children were fed and how the subsequent child is fed.<sup>26</sup> This correlation suggests the crucial importance of supporting a primiparous patient for successful breast-feeding as it will influence feeding patterns for later children as well.<sup>28, 32</sup>

The mother's decision. Many women have already decided on the method of infant feeding before pregnancy<sup>24, 26</sup> and almost all have decided by the last trimester of pregnancy. Thus, information given during obstetric care is much more important than any pediatric pleadings after birth. Mothers report re-

ceiving information and advice from a variety of sources. 17. 21. 24. 30 The reasons women choose to start breast-feeding center around the recognition of health benefits for the baby, the closeness possible between mother and child, and the belief that it is "the natural thing" to do. The reasons for which mothers bottle-feed also are complex, but the proportion of these mothers expressing fear and embarrassment about breast-feeding is high (in some cases over 50%). 17. 18. 24, 26 Also of concern is the proportion of women who are unaware of any differences between breast- and bottle-feeding or who have simply never thought about breast-feeding. 33

Although many writers glibly state that salaried work causes women to reject breast-feeding, the contention that work is a major impediment is not sustained by empirical evidence. <sup>17, 24, 34–36</sup> No study of the impact of work on breast-feeding suggests this as an important consideration for more than 10% of the population surveyed, and it is frequently for far less. <sup>17, 18, 21, 24, 26, 37</sup> There is some evidence that working women breast-feed more than nonworking women. <sup>35, 38</sup>

The most commonly cited reason for mothers who are nursing to stop is that the milk "dries up" or is insufficient. 17. 21. 24. 30 Helsing 99 emphasizes that this answer is commonly cited because it is socially acceptable. Applebaum 40 and Gurney 41 stress that where milk is, in fact, insufficient this is frequently caused by inappropriate advice and faulty technique—usually the introduction of supplementary feeds that reduce sucking on the breast and thus reduce milk secretion. Other factors which have been noted as contributing to discontinuation are fatigue, sore nipples, and medical advice to discontinue breast-feeding.

#### Interventions

A recent resurgence of breast-feeding in Western countries has come about, in part, as a result of three forces: the activities of breast-feeding support groups<sup>19, 42</sup>; a "back-to-nature movement," in which consumers spurn artificial or processed foods; and growing appreciation of and advocacy for breastfeeding by some health professionals. In the 1970s, there was a virtual explosion of interest in breastfeeding: More than 150 papers on human milk and the process of breast-feeding appeared in the last 9 months of 1976 alone. 43 Beyond these general phenomena are specific program efforts undertaken in an attempt to increase the incidence and duration of breast-feeding. Some of these have taken place at the national level (e.g., in England and Sweden) while most were implemented at the hospital level. Overall, there is impressive evidence demonstrating that rates of breast-.. feeding can be increased.

Medical interventions which have proved effective in promoting breast-feeding can be divided into two categories: those that supply information and support and those that change hospital routines so as to facilitate the successful establishment of lactation. In many cases, successful programs to increase breast-feeding have involved both types of actions, which seem to have the potential for interacting synergistically. Indeed, increased information on the importance of breastfeeding may influence hospital staff to change hospital routines because the staff itself has become more supportive of breast-feeding. Such positive staff attitudes also may be translated into direct support of patient decisions to breast-feed even without a formal patienteducation program. To the extent that the data permit, however, information/support programs and hospital routine changes will be considered separately since they have different practical implications: The first set of activities involves changes in the behavior of personnel toward patients while the second involves changes in the management of hospital services.

Information and support. Theoretically, activities providing information and those providing support are different from each other and separable in their effects. In fact, the two types of activities are almost impossible to separate. In the first place, all educational exchanges involve nonformal, unspoken messages of support from health personnel to patients, and these messages seem valuable in promoting breast-feeding. Second, imparting information to patients requires increased staff time in direct patient contact, and this too has emotionally supportive effects. Finally, training of staff so that they can teach patients has the effect of increasing staff knowledge-and often enthusiasmabout the benefits of breast-feeding. The impact of any educational program may thus derive as much from the support offered as from the technical information given. The close interaction of information and support is demonstrated in studies where the efficacy of technical advice in solving common problems can be evaluated separately from the effect of the intervention in toto in promoting lactation. For example, while breast-feeding classes do favor a longer duration of nursing, the breast preparation taught in those very classes, contrary to expectations, is not effective in preventing sore nipples or breast engorgement.44 Similarly, it was found that it was not nipple preparation per se but the extra support and encouragement provided to an experimental group that accounted for their better nursing experiences. 45, 46

Some of the earliest programs to increase breast-feeding consisted of combined information and support. Because artificial feeding resulted in catastrophic

episodes of infectious diseases, 47-50 physicians in the first decades of the twentieth century were concerned with promoting breast-feeding in order to reduce infant morbidity and mortality. One of the first programs to promote breast-feeding took place in Minneapolis, Minnesota.72 There, two doctors established a Breastfeeding Investigation Bureau, which enlisted the cooperation of every physician in the city, assigned a nurse to visit the home of every mother within 3 weeks of a birth, and solicited information by mail on each nursing mother and her child. While no comparisons can be made with breast-feeding rates before the Bureau's work began, the doctors cite a fall in the city's infant mortality rate from 81 to 65 per thousand as evidence of their success in promoting breast-feeding. Among babies born in the first 5 months of 1919, 96% were breast-fed after 2 months, and 72% were still receiving breast milk after 9 months. A similar system was adopted in Nassau County, New York, in 1923:52 Nine tenths of the mothers breast-fed their infants for 1 month and two thirds continued for at least 7 months. Again, while no comparative data from earlier years are available, the authors note that the infant mortality rate in this group was 49 per thousand, as compared with 70, 67, and 78 per thousand in the immediately preceding years of 1920, 1921, and 1922.

A wide variety of recent studies confirms the principle that mothers afforded reliable information from health workers are more likely to initiate and continue breast-feeding. Wood<sup>53</sup> notes that women choosing breast-feeding have the largest number of sources of information. In one sample, only a third of new mothers felt that hospital nurses provided useful information, yet among those women who felt that the information they had received was useful, 79% were still breast-feeding at 3 months post partum, more than twice the average for the whole group. The main difference between those who were successful at breast-feeding and those who were not seemed to be the women's access to support and information.<sup>22</sup>

Another striking finding is that information and education programs aimed at hospital staff are often as effective in increasing breast-feeding rates as direct education of new parents. Promoting breast-feeding among relevant health personnel seems to be the first step in creating a service atmosphere that is truly conducive to successful lactation. This argues for better training of all staff and reinforcement of breast-feeding messages from obstetricians, in particular, to other personnel with whom they work. A single ward seminar designed to increase the interest in and knowledge of the nursing staff succeeded in increasing the proportion of mothers breast-feeding on hospital dis-

charge from 14% to 37%.<sup>30</sup> When this study was repeated 2 years later,<sup>29</sup> the proportion of women breast-feeding on discharge had risen to 52%, with a longer duration of breast-feeding and a noticeable delay in the introduction of solid foods. Smart and Bamford<sup>54</sup> noted an increase in breast-feeding upon hospital discharge from 37% to 44% over a few months without any specific patient-oriented program. They attributed this rise in part to the fact that their own research had stimulated great interest in breast-feeding among the health staff.

Continuity of medical care also seems to be an important factor in providing the background of information and support necessary for successful lactation. Two groups, both seen in the same antenatal clinic, were noted to have markedly different breast-feeding rates. Among those seeing general practitioners who personally provided all the prenatal, labor and delivery, and postnatal care for each of their patients, breast-feeding was practiced by 69% at 6 weeks post partum. Those seen by specialist obstetricians, on the other hand, were given prenatal care by a shared, group practice arrangement and were seen in the hospital by a number of different house physicians. This second group had a breast-feeding rate of only 32% at 6 weeks post partum. 55

Physicians as individuals can exercise a great deal of influence on breast-feeding, both positively<sup>56</sup> and negatively.22 An American obstetrician in Indiana promotes breast-feeding by convening her patients in an informal group discussion. Each expectant mother is assigned a "counselor" who herself is an experienced breast-feeding mother. In 2 years, the hospital breastfeeding rate of these patients increased from 33% to 65%, and the proportion breast-feeding at 5 months increased from 15% to 52%.57 Haider58 shows that with a minimal investment of time in a group discussion conducted by a physician for 20 to 30 parents, 80% of those attending breast-feed as compared with only 20% of those who do not attend. When talks are given in smaller groups, 90% of women breast-feed in the hospital and 80% continue for at least 3 months.

Although it is clear that good information and support networks can increase the prevalence of successful breast-feeding, the proportion of women receiving ittle or no advice from professional sources is surprisingly high. Many women are acutely aware of the failure of professional sources to provide information. <sup>24,44,58</sup> In one group of mothers, only 8% had been given specific information on breast-feeding at their antenatal clinic<sup>26</sup>; of these, 91% attempted to breast-feed, far more than those given little or no advice. Seventy-eight percent of bottle-feeders reported they had been given

no encouragement to breast-feed; even among breast-feeders, only 42% said they had been encouraged to do so. Even when women acknowledge professional support, most rank the help of the doctor below that of the nurse or midwife.59 Women apparently feel that doctors are frequently unsupportive,32 and if doctors are discouraging about breast-feeding, mothers will be discouraged from attempting it.25 Taken together, all these studies provide evidence for the general hypothesis that information and support can significantly enhance the chances for successful breast-feeding. While the types, timing, and duration of programs will need to be tailored to suit each locale, it is clear that health personnel play an important role in fostering the conditions in which breastfeeding can flourish.

Changes in hospital routines. Technological progress has permitted enormous advances in the care of sick and abnormal infants, but routine hospital procedures for healthy infants, in many cases, appear to interfere with normal physical and psychological processes. In particular, many hospital routines have been shown to decrease the likelihood of successful initiation and maintenance of lactation. Revision of these routines can increase the incidence of positive breast-feeding experiences. Anything that restricts feeding contact during the first 10 days of life is associated with less successful breast-feeding. 60. 61 Included are separation of mother and baby after birth, introduction of prelacteal feeds and/or supplementary feeds, feeding on a rigid schedule, and drugs administered in labor.

Immediate breast-feeding and skin-to-skin contact. A number of studies point toward the primary importance of sustained intimate contact between mother and infant in the first postpartum days. 10, 11, 62, 63 Mothers permitted such contact show greater affectionate behavior, adaptability, and independence when compared to mothers deprived of this experience. There is a significant and growing body of evidence suggesting that skin-to-skin contact between mother and child immediately after delivery strengthens the mother-child bond, one consequence of which is greater likelihood of prolonged breast-feeding. Studies from distinctively different population groups support this hypothesis. In Guatemala, the pioneering work of Klaus and Kennell<sup>10</sup> demonstrated that 45 minutes of contact after birth was significantly associated with a greater duration of breast-feeding, up to 100% longer than in the control group. Infants in the experimental group suffered fewer episodes of infectious disease, and in one trial infants in the experimental group gained more weight at 6 months and 1 year than the control group infants.64

De Chateau<sup>65</sup> found that providing 30 minutes of skin-to-skin contact immediately after birth resulted in a breast-feeding rate of 58% at 3 months, as compared with 26% in the control group. The effect of early mother-child contact was also demonstrated by a small controlled trial in the United States.66 Of 12 mothers intending to breast-feed, six were given their babies shortly after birth while the other six were given their babies 16 hours later. At 2 months post partum, all six of the early contact mothers were still breast-feeding, while only one of six in the delayed contact group was doing so. Similar results were found in a Swedish study of the effect of early skin-to-skin contact and sucking on breast-feeding patterns.67 The median duration of breast-feeding in the early contact group was 175 days, over 2 months more than the median duration of 108 days in the control group mothers. Significant benefits of early initiation of breast-feeding combined with increased frequency of nursing also has been demonstrated.68 A group of mothers who nursed early and breast-fed every 2 hours continued feeding for a median of 182 days, as compared to 77 days for a group who initiated breast-feeding later and fed only every 4 hours. The early initiation of sucking was found more important in prolonging breast-feeding than the increased frequency of feeding.

While immediate skin-to-skin contact and early sucking are powerful promoters of successful breastfeeding, cross-cultural studies show that in very traditional societies, where breast-feeding is the norm, successful lactation may occur without immediate sucking.20, 69 In such situations, however, many other extremely powerful stimuli to successful breast-feeding also are at work. This lends weight to the conclusion that "early contact may be a simple way of promoting breast-feeding for some mother-infant pairs cared for in the highly technical and 'unnatural' environment of today's delivery units."70 The diversity of possible pathways to successful breast-feeding-and mothering-speaks to the flexibility and adaptability of the human species. Still, there need to be mechanisms by which mother-infant attachment is facilitated, whether these are built into the general social structure or specifically provided by a technologically oriented birthcare system.

Rooming-in. Rooming-in (keeping the newborn infant within easy reach of the mother 24 hours a day) also has been shown to increase the likelihood of successful breast-feeding. A detailed analysis of the effects of rooming-in on the incidence and duration of breast-feeding showed that as late as 3 to 4 months after delivery about 1¾ times as many "rooming-in" mothers as "nursery" mothers were still breast-feeding.<sup>71</sup> Similar

results were reported by Lind and Jaderling<sup>72</sup> in 1964 in a trial with 172 rooming-in mothers and 172 control mothers. In a Swedish study of 3,214 mothers, 93% of mothers who had had rooming-in were breast-feeding upon hospital discharge as compared with 76% of mothers from the regular maternity ward.73 Mothers who had rooming-in also showed more self-confidence in the management of their children and sought advice less often in the first month post partum. The institution of compulsory rooming-in in Durham, North Carolina, boosted the breast-feeding rate there from 35% to 58.5% upon hospital discharge.74 While no significant correlation was found between room arrangements and intention to breast-feed, two thirds of those mothers who were still breast-feeding at 3 months post partum had had rooming-in arrangements while more than half of the mothers who had stopped breastfeeding at this time had not.22

Programmatically, the advantages of early contact between mother and child and 24-hour rooming-in are often combined. Sousa and associates75 showed that among mother-infant pairs who enjoyed these arrangements, 77% were still breast-feeding at 2 months post partum, as compared to 27% of the control group in which mothers and babies were separated according to hospital routine. In the Philippines, Clavano<sup>76</sup> reorganized the postpartum ward of one hospital to provide rooming-in for all mothers and newborn infants. Mothers were given their infants within 2 hours after birth and were not separated from their infants while in the hospital. In addition to an increase in the percentage of women breast-feeding from 26.4% to 87.3%, in the infant population there was a reduction in the morbidity rate of 56.8% and in the mortality rate of 44.9%, mostly because of decreases in septicemia and diarrhea.

As demonstrated by the decline in morbidity and mortality in Clavano's<sup>76</sup> study, rooming-in appears to offer substantial benefits in reduction in the risk of infection. It also may reduce the amount of staff time needed for infant care since the mothers provide most of the care for their own babies. It seems to increase the confidence and independence of mothers<sup>10, 62</sup> and, above all, to foster a healthy relationship between mother and newborn infant in the sensitive period following birth. Furthermore, the rooming-in model has been demonstrated to be overwhelmingly preferred by mothers.<sup>62</sup>

Demand feeding with no supplementary bottles. A close concomitant of early initiation of breast-feeding and rooming-in is demand feeding, in which the baby is allowed to nurse whenever it desires rather than according to a rigid schedule. Apparently, demand feed-

ing can be instituted as part of the normal hospital routine with little difficulty.77 Consistently, breastfeeding has been found more likely to be successful among infants on demand feeding. 78, 79 A sensitive, dynamic interaction between mother and child governs the normal hormonal control of milk secretion (prolactin) and milk ejection (oxytocin). Feeding according to a rigid schedule inhibits natural interactions and the early successful establishment of lactation80 at least three separate ways. Interference with normal hunger/satiety cycles in the infant may disrupt the mechanisms for regulation of food intake; decreased frequency and effectiveness of infant sucking will interfere with prolactin production and, therefore, the milk supply of the mother; finally, rigid routines increase anxiety in the mother and interfere with milk ejection.

Evidence is mounting that the mechanisms for self-regulation of food intake in the infant are sensitive and effective. 81 Both small-for-date and large-for-date breast-fed infants tend to "grow back into the charts" more quickly than their bottle-fed counterparts. 32 These same mechanisms of intake regulation, when undisturbed, also have been reported to decrease the likelihood of infantile obesity. 83

The routine administration of prelacteal feeds and subsequent complementary feeds to the breast-fed infant reduce the infant's sucking on the breast and hence the secretion of milk. 59 Furthermore, since sucking a bottle is a fundamentally different process from sucking a breast, complementary feeds also may undermine lactation by making the infant's sucking motions inappropriate for breast-feeding. This hypothesis is supported by a study of 884 infants in which the duration of breast-feeding was doubled if supplementary feedings were introduced by spoon rather than bottle. 84

The undesirable effects of complementary feeding include not only the physiologic inhibition of milk secretion due to decreased sucking but also the implicit undermining message to the mother: The staff feels she cannot meet the baby's needs by herself. This message also may be conveyed by other rigid procedures with equally deleterious effects. This may be the mechanism whereby routine weighing of babies before and after each breast-feeding inhibits successful lactation.67 Abandonment of this routine was found to reduce early lactation failure, probably by decreasing anxiety that blocks the milk "let-down reflex." In fact, prelacteal feeds have been found useless to prevent wright loss in the newborn infant; what they more commonly prevent is successful breast-feeding.<sup>70</sup> Supplementary feeds may have the same effect. When women complain of insufficient milk, a problem with many possible causes, they are often counseled to add artificial feeds. The offer by physicians of a "prescription" of bottle supplements without investigation of the cause of the mother's complaint is an unusual deviation from normal standards of medical care. In a study of patient-physician interactions, it was found that women who complained of "insufficient milk" were counseled to add complementary feeds, with the result that breast-feeding stopped within 2 weeks in every case.<sup>55</sup>

Drugs. Certain drugs given to mothers may inhibit the establishment of successful lactation. 40 Brazelton 85, 85a demonstrated that the ability to breast-feed successfully was impaired by the administration of barbiturates to the mother during labor. On the first postpartum day, 30% of heavily medicated mothers were considered "effective" breast-feeders, as compared to 65% of lightly medicated mothers. It took 5 to 6 days before this difference disappeared. Using more precise measurements of sucking, Kron and co-workers86 demonstrated that central nervous system depressants given during labor reduce the amount of nutritive sucking by the infant. Decreased sucking leads to decreased consumption of milk by the infant and decreased stimulus for milk production in the mother. Medication given in labor can inhibit sucking and render feeding interactions more difficult for up to 10 days post partum.87 It has also been shown that ergonovine maleate interferes with prolactin secretion and thus may decrease milk production.88

Preliminary evidence from Thailand indicates that the timing of postpartum sterilization may have significant effects on lactation, either because of the anxiety and stress caused by the procedure or because of the use of sedation and anesthesia. Milk production was apparently not affected in women undergoing operation within 24 hours of delivery, but there was a significant lowering of milk volume at both 7 and 14 days post partum in mothers whose tubal ligations were done 4 to 6 days after delivery. The investigators hypothesize that the lactation-suppressing effects of drugs and anxiety are most critically significant if imposed on mothers during the time when milk production begins and lactation is being established.

The evidence demonstrates that certain routine medical practices and procedures can have deleterious effects on lactation. The effects of many other practices on breast-feeding, even those thought to be totally unrelated to lactation, remain completely unknown. Certainly, it cannot be assumed that routine patient care practices are entirely benign in their effects on mother-infant interactions. Until questions are asked about the effects of routine practices, however, their

exact impacts on nursing performance will never become evident.

Information combined with changed hospital practices. Just as combining information and support enhances breast-feeding more than either one alone, combining both with sensible hospital routines should act as an even more powerful promoter of breastfeeding success. In Sheffield, England, a package of changes, including better education of doctors and nurses, public education, antenatal classes, modification of hospital routines, and better home help to mothers from midwives and nurses, was instituted. The result was an increase in the proportion of women intending to breast-feed from 36% in 1973 to 59% in 1976.90 In a prospective study in Singapore, Wong91 showed that 72% of mothers initiated breast-feeding in a ward where nurses and midwives enthusiastically promoted it and where supplementary feeding was halted. In a comparable ward, where staff had no more than routine interest and powdered infant formula was supplied on demand, only 47% of mothers initiated breast-feeding.

#### Implications for actions to promote breast-feeding

Breast-feeding is a complex interaction between mother and infant that can be enhanced or inhibited by a wide range of social, psychological, and physiologic factors. While the overall social context and the value that each culture places on breast-feeding may ultimately determine infant feeding patterns, medical personnel have both the responsibility and the opportunity to increase the status of breast-feeding within the professions as well as in the community. The evidence cited above demonstrates that breast-feeding promotion activities work in all social environments and systematically raise the prevalence and duration of breast-feeding, whether these were initially low or high. For example, in Sweden, a high breast-feeding rate was made almost universal (76% to 93%), whereas in Brazil interventions converted a low rate into a high rate (27% to 77%).73, 75

In this paper, interventions that have been shown to be successful are classified into two broad categories: information and support and hospital routines. In general, the first type of change is most likely to meet with the greatest acceptance from health workers. Few members of the health team have vested interests in "no education," and none would oppose actively the provision of information. The absence of education in most hospitals is usually ascribed to heavy patient loads, but this is merely a reflection of its low priority in most service delivery systems: With a medical orientation

toward unusual pathology, normal lactation is seldom found "interesting."

In the case of hospital routines, however, the situation is different: "Hospital routines are often much more geared to the requirements of the institution than to the needs of mother and infant."27 Changing routines, even when the overwhelming weight of evidence shows clear benefits to patients, encounters initial resistance from those accustomed to standard procedures. Ironically, although it is easier to gain administrative and staff support for educational activities than for institutional changes, the latter may be easier and cheaper to accomplish. Education programs require ongoing staff commitment, repeated effort every year, and recurrent funds. Changes in hospital practices, on the other hand, generally can be accomplished in a short period of time, need be done only once, do not require continued efforts, and often end up saving money.76

Given the current pressures on medical care to (1) encourage self-reliance, (2) promote physical and psychological health through preventive rather than curative medicine, and (3) contain costs, the promotion of breast-feeding offers exciting possibilities. In the immediate future there are a number of steps that can contribute to the promotion of breast-feeding, and these do not require unreasonable amounts of staff time, expensive pedagogic materials, or elaborate architectural renovations. The data suggest that even minimal expressions of interest by physicians in breastfeeding (e.g., ward seminars, research projects, simply inquiring how many women are breast-feeding) can make a difference. Similarly, reorganization of hospital routines in the perinatal period, with an eye to minimizing interventions and practices of questionable value, could enhance the well-being of mother and infant.

The burden of responsibility for promoting breast-feeding has fallen on pediatricians because they treat illnesses arising out of improper feeding. Good pediatric guidance is, of course, essential if breast-feeding is to be sustained through minor physical and psychological problems. However, if a mother is not convinced of the superiority of breast-feeding, she may not even try it in the first instance: Positive attitudes toward breast-feeding are correlated with significantly higher success rates than ambivalent or negative attitudes. By the time a pediatrician sees the mother, it is too late to provide the information and encouragement that enhance the chances for successful nursing. It is the obstetrician who, in fact, has the greatest potential for increasing the prevalence and duration of breast-feeding.

Because of the state of the art of breast-feeding re-

search, there are certain important things which we do not yet understand. Although it is clear that both information/support and appropriate medical practices will increase breast-feeding rates, we do not yet know anything about optimum mixes of these two sorts of interventions. It is not known how much of each must be provided for maximum efficacy and efficiency of program operation, although it is clear that there is some substitutability of effect. For example, while late initiation of breast-feeding is not detrimental to successful lactation in certain traditional societies, it obviously has adverse effects in Western-oriented medical systems. How much support and education would be necessary to overcome this barrier to nursing? Would it be easier and/or cheaper to make universal changes in postdelivery practices than to provide information and support networks? The answers to such questions are not immediately available.

Neither is it known how to compute the exact costs and/or savings involved in revision of hospital routines. Although it is clearly not an expensive proposition, and may be money saving, to make such changes, figures applicable to United States institutions with different service provision patterns are not available at present. Both the financial and service mix questions have important implications for rational program development, and, although the answers are not yet known, there is no reason to suppose that they are unknowable. What is apparent is that staff attitudes and hospital routines can be structured rather easily and effectively so that they make important contributions to successful lactation.

#### REFERENCES

- 1. Cunningham, A. S.: Morbidity in breast-fed and artifi-
- cially-fed infants, J. Pediatr. 90:5, 1977. Ironside, A. G., Tuxford, A. F., and Heyworth, B.: A survey of infantile gastroenteritis, Br. Med. J. 3:20, 1970.
- 3. Larson, S. A., Jr., and Homer, D. R.: Relation of breast versus bottle feeding to hospitalization for gastroenteritis in a middle-class U.S. population, J. Pediatr. 92:417,
- 4. Breastfeeding and the Mother, Ciba Foundation Symposium, 45 (new series), Amsterdam, 1976, Elsevier Publishing Co.
- 5. Chandra, R. K.: Immunological aspects of human milk Nutr. Rev. 36:265, 1978.
- 6. Hambraeus, L.: Proprietary milks versus human breasmilk. A critical approach from the nutritional point of view, Pediatr. Clin. North Am. 24:17, 1977.
- Jelliffe, D. B., and Jelliffe, E. F. P.: Human Milk in the Modern World, Oxford, 1978, Oxford University Press
- 8. Mosley, W. H., editor: Nutrition and Human Reproduction, New York, 1978, Plenum Press.
- Newton, N.: Psychologic differences between breast and bottle feeding, Am. J. Clin. Nutr. 24:993, 1971.
- Klaus, M. H., and Kennell, J. H.: Maternal-Infant Boncing, St. Louis, 1976, The C. V. Mosby Company.
- 11. Lozoff, B., Brittenham, G. M., Trause, M. A., Kennell. J. H., and Klaus, M. H.: The mother-newborn relationship: limits of adaptability, J. Pediatr. 91:1, 1977.
- 12. Vahlquist, B.: The evolution of breast feeding in Europe, . Trop. Pediatr. 21:11, 1975.
- 13. Meyer, H. F.: Breast feeding in the United States, Clin. Pediatr. 7:708, 1968.
- 14. Hofvander, Y., and Petros-Barvazian, A.: WHO collazorative study on breast feeding, Acta Paediatr. Scand. **67:**556, 1978.
- 15. Berkelhamer, J. E., Whitham, R. H., and North, J. J.: Distorted conceptions of infant nutrition among urban mothers, Clin. Pediatr. 16:986, 1977.
- 16. Jelliffe, D. B., and Jelliffe, E. F. P.: Doulas, confidence, and the science of lactation, J. Pediatr. 84:462, 1974.
- 17. Bacon, C. J., and Wylie, J. M.: Mothers' attitudes to infant feeding at Newcastle General Hospital in summer 1975, Br. Med. J. 1:308, 1976.

- 18. Evans, N., Walpole, I. R., Qureshi, M. U., et al.: Lack of breast feeding and early weaning in infants of Asian immigrants to Wolverhampton, Arch. Dis. Child 51:608, 1976
- 19. Meera, H.: La Leche League in the United States: a key to successful breast-feeding in a non-supportive culture, J. Nurs. Midwif. 21:20, 1976.
- 20. Raphael, D.: The lactation-suckling process within a matrix of supportive behavior, Ph.D. thesis, Columbia University, 1966.
- 21. Brimblecombe, F. S. W., and Cullen, D.: Influences on a mother's choice of method of infant feeding, Public Health (Lond.) 91:117, 1977.
- 22. Cole, J. P.: Breast-feeding in the Boston suburbs in rela-
- tion to personal social factors, Clin. Pediatr. 16:352, 1977. 23. Coles, E. C., Cotter, S., and Valman, H. B.: Increasing prevalence of breast-feeding, Br. Med. J. 2:1122, 1978.
- 24. Eastham, E., Smith, D., Poole, D., et al.: Further decline of breast-feeding, Br. Med. J. 1:305, 1976.
- 25. Halpern, S. R., Sellars, W. A., Johnson, R. B., et al.: Factors influencing breast-feeding: notes on observations in Dallas, Texas, South. Med. J. 65:100, 1972.
- 26. Jones, R. A. K., and Belsey, E. M.: Breastfeeding in an inner London borough: a study of cultural factors, Soc. Sci. Med. 11:175, 1977.
- 27. Richards, M. P. M.: Feeding and the early growth of the mother-child relationship, Mod. Probl. Paediatr. 15:143,
- 28. Sacks, S. H., Brada, M., Hill, A. M., et al.: To breast feed or not to breast feed. A survey of primiparae, Practitioner 216:183, 1976
- 29. Sloper, K. S., Elsden, E., and Baum, J. D.: Increasing breast feeding in a community, Arch. Dis. Child. 52:700,
- 30. Sloper, K., McKean, L., and Baum, J. D.: Factors influencing breast-feeding, Arch. Dis. Child. 50:165,
- 31. Call, J. D.: Emotional factors favoring successful breast feeding of infants, J. Pediatr. 55:485, 195.
- Martin, J.: Infant Feeding 1975: Attitudes and Practices in England and Wales, London, 1978, Her Majesty's Stationery Office.

- 33. Creery, R. D. G.: Breast feeding, Br. Med. J. 2:239, 1973.
- Berg, A.: The crisis in infant feeding practices, Nutr. Today 12:18, 1977.
- 35. Rumeau-Rouquette, C., and Crost-Deniel, M.: France case study: breast-feeding during the neo-natal period in France, Conference on Lactation, Fertility and the Working Woman, Bellagio, Italy, July 5-12, 1977.
- Winikoff, B.: Nutrition, population, and health: some implications for policy, Science 200:895, 1978.
- Almroth, S.: Breast feeding practices in a rural area of Jamaica, masters thesis, Cornell University, 1976.
- Deschamps, J. P.: Allaitement maternal, in Nutrition et Alimentation du Nouveau-ne, Monaco, 1978. Societe Nestle.
- 39. Helsing, E.: Lactation education: the learning of the "obvious," in Breastfeeding and the Mother, Ciba Foundation Symposium, 45 (new series), Amsterdam, 1976, Elsevier Publishing Co.
- 40. Applebaum, R. M.: The obstetrician's approach to the breasts and breastfeeding, J. Reprod. Med. 14:98, 1975.
- Gurney, M.: Establishment of lactation, Br. Med. J. 1:1467, 1976.
- 42. Thomson, M.: The role of voluntary agencies in promoting breastfeeding, in Symposium on Breastfeeding, J. Trop. Pediatr. 21:260, 1975. (Monogr. No. 43.)
- 43. Jelliffe, D. B., and Jelliffe, E. F. P.: Breast feeding is best for infants everywhere (some factual reasons), Nutr. Today 13:12, 1978.
- 44. Whitley, N.: Preparation for breastfeeding: a one-year followup of 34 nursing mothers, JOGN Nurs. 7:44, 1978.
- Waller, H.: The early failure of breast feeding, Arch. Dis. Child. 21:1, 1946.
- Blaikley, J. B., Clarke, S., MacKeith, R., and Ogden, K. M.: Breast-feeding: factors affecting success; report of trial of Woolwich methods in group of primiparae, Br. J. Obstet. Gynaecol. 60:657, 1953.
- Davis, W. H.: Statistical comparison of the mortality of breast-fed and bottle-fed infants, Am. J. Dis. Child. 5:234, 1922.
- 48. Grulee, C. G., Sanford, H., and Herron, P. H.: Breast and artificial feeding: influence on morbidity and mortality of twenty thousand infants, JAMA 103:735, 1934.
- 49. Howarth, W. J.: The influence of feeding on the mortality of infants, Lancet 1:210, 1905.
- Woodbury, R. M.: The relation between breast and artificial feeding and infant mortality, Am. J. Hyg. 2:668, 1922.
- 51. Sedgwick, J. P., and Fleischner, E. C.: Breast feeding in the reduction of infant mortality, Am. J. Public Health 11:153, 1921.
- 52. Richardson, F. H.: Universalizing breast feeding in a community, JAMA 85:668, 1925.
- Wood, C. B. S., in discussion of Sjolin, S.: Present trends in breast feeding, Curr. Med. Res. Opin. Suppl. 1 4:24, 1976.
- 54. Smart, J. L., and Bamford, F. N.: Breast-feeding: "spontaneous" trends and differences, Lancet 2:42, 1976.
- 55. Burne, S. R.: Breast feeding, Lancet 2:261, 1976.
- Kimball, E. R.: Breast feeding in private practice, Q. Bull. Northwest Univ. Med. School 25:257, 1951.
- 57. Newton, N.: Key psychological issues in human lactation, in Waletzky, L., editor: Proceedings of Symposium on Human Lactation, October 7, 1976, Office of Maternal and Child Health, Department of Health, Education, and Welfare, Washington, D. C., U. S. Government Printing Office. In press.
- Haider, S. A.: Encouragement of breast-feeding, Br. Med. J. 1:650, 1976.
- Gillie, L.: Difficulties and discouragements encountered by mothers, J. Hum. Nutr. 30:248, 1976.

- Gurney, M.: Establishment of lactation, Br. Med. J. 1:1467, 1976.
- Richards, M. P. M.: Feeding and the early growth of the mother-child relationship, Mod. Probl. Paediatr. 15:143, 1975.
- 62. Greenberg, M., Rosenberg, I., and Lind, J.: First mothers rooming-in with their newborns: its impact upon the mother, Am. J. Orthopsychiatry 43:783, 1973.
- 63. Klaus, M. H., Jerauld, R., Kreger, N. C., et al.: Maternal attachment. Importance of the first post-partum days, N. Engl. J. Med. 286:460, 1972.
- 64. Sosa, R., Klaus, M., Kennell, J. H., and Urrutia, J. J.: The effect of early mother-infant contact on breastfeeding, infection and growth, in Breastfeeding and the Mother, Ciba Foundation Symposium, 45 (new series), Amsterdam, 1976, Elsevier Publishing Co.
- 65. De Chateau, P.: Neonatal care routines; influences on maternal and infant behavior and on breast feeding, thesis, Umea, Sweden, Umea University medical dissertations, N.S. No. 20, 1976.
- Johnson, N. W.: Breast-feeding at one hour of age, Am. J. Mat. Child Nurs. 1:12, 1976.
- 67. De Château, P., Holmberg, H., Jakobsson, K., and Winberg, J.: A study of factors promoting and inhibiting lactation, Dev. Med. Child Neurol. 19:575, 1977.
- 68. Salariya, E. M., Easton, P. M., and Cater, J. I.: Duration of breast-feeding after early initiation and frequent feeding, Lancet 2:1141, 1978.
- 69. Hull, V. J.: A study of birth interval dynamics in rural Java, in Mosley, W. H., editor: Nutrition and Human Reproduction, New York, 1978, Plenum Press.
- 70. Strong, R. A.: Rooming-in the newborn with its lying-in mother, Diplomate 21:301, 21:301, 1949.
- 71. Jackson, E. B., Wilkin, L. C., and Auerbach, H.: Statistical report on incidence and duration of breastfeeding in relation to personal social and hospital maternity factors, Pediatrics 17:700, 1956.
- Lind, J., and Jaderling, J.: The influence of "rooming-in" on breast feeding, Acta Paediatr. (Uppsala) (Suppl.) 159:1, 1964.
- Bjerre, J., and Ekelund, H.: Breastfeeding and postpartum care, Acta Paediatr. (Uppsala) (Suppl.) 206:125, 1970.
- McBryde, A.: Compulsory rooming-in on the ward and private newborn service at Duke Hospital, JAMA 145: 625, 1951.
- 75. Sousa, P. L. R., et al.: Attachment and lactation, presented at the Fifteenth International Congress of Pediatrics, Buenos Aires, October 3, 1974.
- 76. Clavano, N.: Personal communication, 1978.
- Cruse, P., Yudkin, P., and Baum, J. D.: Establishing demand feeding in hospital, Arch. Dis. Child. 53:76, 1978.
- Illingworth, R. S., Stone, D. C. H., Jowett, G. H., and Scott, J. F.: Self-demand feeding in a maternity unit, Lancet 1:683, 1952.
- 79. Olmstead, R. W., and Jackson, E. B.: Self-demand feeding in the first week of life, Pediatrics 6:396, 1950.
- McNeilly, A. S., and McNeilly, J. R.: Spontaneous milk ejection during lactation and its possible relevance to success of breast-feeding, Br. Med. J. 2:466, 1978.
- 81. Hall, B.: Changing composition of human milk and early development of an appetite control, Lancet 1:779, 1975.
- Ounsted, M., and Sleigh, G.: The infant's self-regulation of food intake and weight gain, Lancet 1:1393, 1975.
- Shukla, A., Forsyth, H. A., Anderson, C. M., et al.: Infantile overnutrition in the first year of life: a field study in Dudley, Worcestershire, Br. Med. J. 4:507, 1972.
- Ungar, R.: Zwiemilchnahrung und Stilldauer, Kinderaerztl. Prax. 17:295, 1949.
- 85. Brazelton, T. B.: Psychophysiologic reactions in the neo-

- nate. I. The value of observation of the neonate, J. Pediatr. 58:508, 1961.
- 85a. Brazelton, T. B.: Psychophysiologic reactions in the neonate. II. Effect of maternal medication on the neonate and his behavior, J. Pediatr. 58:513, 1961.
- Kron, R. E., Stein, M., and Goddard, K. E.: Newborn suckling behaviour affected by obstetric sedation, Pediatrics 37:1012, 1966.
- 87. Richards, M. P. M., and Bernal, J. F.; Effects of obstetric medication on mother-infant interaction and infant development, in Proceedings of the Third International Congress of Psychosomatic Medicine in Obstetrics and Gynaecology (London, 1971), Basel, 1972, S. Karger AG.
- Gynaecology (London, 1971), Basel, 1972, S. Karger AG.
  88. Canales, E. S., Garrido, J. T., Zárate, A., Mason, M., and Soria, J.: Effect of ergonovine on prolactin secretion and milk let-down, Obstet. Gynecol. 48:228, 1976.
- 89. Dusitsin, N., et al.: The effect of postpartum tubal liga-

- tion on breast-feeding, Chulalongkorn University, Bangkok, Thailand, Unpublished data.
- 90. Jepson, M. E., et al.; Breast-feeding in Sheffield, Lancet 2:425, 1976.
- 91. Wong, H. B.: The role of the medical and health professions in promoting desirable policies and practices, PAG Bull. 5:16, 1975.
- 92. Coles, E. C., and Valman, H. B.: Breast-feeding in Harrow, Lancet 2:583, 1976.
- 93. Kirk, T. R.: Breast-feeding and mother's education, Lancet 2:1201, 1978.
- 94. Rawlins, C.: Personal communication; 1978.
- Sjölin, S.: Present trends in breast-feeding, Curr. Med. Res. Opin. (Suppl. 1) 4:17, 1976.
- Švejcar, J.: Methodisches Vorgehen zur Einleitung und zum Einhalten der Brusternährung des Säuglings, Klin. Paediatr. 189:333, 1977.

#### Copyright information

The appearance of a code at the bottom of the first page of an original article in this JOURNAL indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc., 21 Congress St., Salem, Mass. 01970, (617)744-3350, for copying beyond that permitted by Section 107 or 108 of the U. S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale. For reprint quantities of 50 or more, please contact Publisher.

#### **ITEMS**

#### Diagnostic ultrasound course for sonologists and sonographers

The Department of Diagnostic Ultrasound at the Health Sciences Centre, Winnipeg, Manitoba, Canada, offers two-week educational courses in diagnostic ultrasound. The dates are: September 22-October 3, 1980; November 24-December 5, 1980; April 13-24, 1981; and June 8-19, 1981.

For further information please contact: Ms. Maureen Kostesky, Program Co-ordinator, Section of Diagnostic Ultrasound, 700 William Ave., Winnipeg, Manitoba, Canada R3E OZ3.

#### Modern Management of Endocrinology and Infertility

The San Antonio Obstetrical and Gynecological Society will present a postgraduate symposium, "Modern Management of Endocrinology and Infertility," October 2-4, 1980.

For further information contact: Local Arrangements, Inc., Lankmark Building, Suite 1224, 705 East Houston St., San Antonio, Texas 78205.

#### **Perinatal Infections**

The Third Annual Perinatal Conference, "Perinatal Infections," sponsored by the Medical College of Virginia, Department of Obstetrics and Gynecology, Pediatrics, and Continuing Medical Education, will be held September 26, 1980, at the Holiday Inn I-64 West End, Richmond, Virginia.

For information write: Kathy E. Johnson, Department of Continuing Medical Education, Box 48, MCV Station, Richmond, Virginia 23298.

#### Ninth Annual Meeting: Clinical Symposium on Gynecologic Endoscopy

The American Association of Gynecologic Laparoscopists will present the "Ninth Annual Meeting: Clinical Symposium on Gynecologic Endoscopy," November 18-23, 1980, at the Hyatt Regency New Orleans, New Orleans, Louisiana.

For information please contact: Jordan M. Phillips, M.D., Chairman of the Board, 11239 S. Lakewood Blvd., Downey, California 90241.

#### Infectious Diseases in Clinical Practice

The Fourth Annual Symposium, "Infectious Diseases in Clinical Practice," will be presented January 31–February 7, 1981, in Park City, Utah. The program is presented by the Division of Infectious Diseases, the Department of Medicine, and Extended Programs in Medical Education, University of California School of Medicine, San Francisco, California.

For further information write: Extended Programs in Medical Education, Room 569-U, University of California, San Francisco, California 94143.

#### Ultrasonography Update: 1981

A course entitled "Ultrasonography Update: 1981," will be presented April 15-18, 1981, at the Princess Hotel in Acapulco, Mexico, by the Faculty of the Ultrasound Section of the Department of Radiology of the University of California, San Diego Medical Center. The Program Director is George R. Leopold, M.D.

For information please contact: Mary J. Ryals, Radiology, P. O. Box 2305, La Jolla, California 92038.

#### Progress in Obstetrics and Gynaecology

The Society of Gynaecology and Obstetrics of Nigeria will hold the Second International Congress on "Progress in Obstetrics and Gynaecology," on September 22-26, 1981, at Eko Holiday Inn, Victoria Island, Lagos, Nigeria.

For information write: Professor O. Akinla, Department of Obstetrics and Gynaecology, Lagos, University Teaching Hospital, P. O. Box 12003 Surulere Lagos State, Nigeria.

#### Basic Science in Obstetrics and Gynecology

A Continuing Education Course, entitled "Basic Science in Obstetrics and Gynecology," will be presented October 6-10, 1980, at The University of Texas Medical School, Houston, Texas. It is sponsored by The University of Texas Medical School, Department of Pathology.

For information write: Sarah J. Clegg, Administrative Secretary, Office of Continuing Education, The University of Texas Health Science Center at Houston, P. O. Box 20708, Houston, Texas 77025.

#### **Progesterone and Progestins**

An international symposium, "Progesterone and Progestins," will be held on May 7-9, 1981, in Paris, France (Organizing Committee: W. C. Bardin, P. Mauvais-Jarvis, and E. Milgrom). The official languages of the symposium will be English and French.

Information may be obtained from: Pr. P. Mauvais-Jarvis, Service d'Endocrinologie, Hôpital Necker 149, rue de Sèvres, 75730 Paris Cedex 15, France.

#### Sexual Problems in Everyday Practice

A course, entitled "Sexual Problems in Everyday Practice," will be presented October 29 and 30, 1980. It is sponsored by Mount Sinai Medical Center of Greater Miami.

For further information contact: CME Office, Mount Sinai Medical Center, 4300 Alton Road, Miami Beach, Florida 33140.

#### Sixth Annual Pan-American Medical Seminar

The Sixth Annual Pan-American Medical Seminar (totally in Spanish), sponsored by Mount Sinai Medical Center of Greater Miami, will be presented November 10-14, 1980.

For further information contact: CME Office, Mount Sinai Medical Center, 4300 Alton Road, Miami Beach, Florida 33140.

#### CEA (Carcino-Embryonic Antigen): Its Role as a Marker in the Management of Cancer

The NIH Consensus Development Conference on CEA (Carcino-Embryonic Antigen): Its Role as a Marker in the Management of Cancer, sponsored by the National Cancer Institute, National Institutes of Health, will be presented September 29, 30, October 1, 1980, at the Masur Auditorium, Clinical Center (Building 10), National Institutes of Health, Bethesda, Maryland.

For technical information please contact: Dr. K. Robert McIntire, Chief, Diagnosis Branch, Division of Cancer Biology and Diagnosis, National Cancer Institute, Building 31, Room 3A10, Bethesda, Maryland 20205.

For administrative information please contact: Ms. Yvonne Lewis, Prospect Associates, 11325 Seven Locks Road, Suite 220, Potomac, Maryland 20854.

#### Specialty Review in Obstetrics and Gynecology. Part II: Practical Aspects

A Specialty Review in Obstetrics and Gynecology. Part II: Practical Aspects will be presented September 29-October 4, 1980. It is sponsored by The Cook County Graduate School of Medicine. Course Coordinator is John H. Isaacs, M.D. A.M.A. Category I Credit Hours: 44.

For further information and registration write: 707 South Wood St., Chicago, Illinois 60612.

#### Infections in Obstetric Patients

The Department of Gynecology and Obstetrics of The Johns Hopkins University School of Medicine will present a continuing education course, entitled "Infections in Obstetric Patients," October 23-25, 1980. The course is approved for 18½ credit hours in Category I, AMA and the LCCME. Other appropriate credits have been applied for. Fee: \$125, \$60 for others.

For further information contact: Program Coordinator, Johns Hopkins University, 22 Turner Bldg., 720 Rutland Ave., Baltimore, Maryland 21205.

#### Maternal and Perinatal Care

The Academy of Obstetricians and Gynaecologists of Windsor, Ontario, Canada, under the auspices of The Essex County Medical Society, will hold a Clinic Day on Wednesday, October 15, 1980, on Maternal and Perinatal Care. The meeting will be held in the Cleary Auditorium, Windsor, Ontario.

Further information may be obtained from: Dr. W. K. Lai, M.D., F.R.C.S., 1368 Ouellette Ave., Windsor, Ontario, Canada N8X 1J9.

#### Seminars in Obstetrics and Gynecology

A series of Seminars in Obstetrics and Gynecology, presented by the GYN CME Fund, will be held at the Dunes Hotel and Country Club in Las Vegas, Nevada. The Seminars are:

- 1. Problems in Perinatology, September 13, 1980
- 2. Endoscopy in OB/GYN, October 4, 1980
- 3. Reproductive Endocrinology, November 15, 1980
- 4. Problems of Peri-Menopause, December 13, 1980 For information write: GYN CME Fund, Inc., 3201 So. Maryland Parkway, Suite 205, Las Vegas, Nevada

So. Maryland Parkway, Suite 205, Las Vegas, Nevada 89109.

#### Campos da Paz Award of the Brazilian Society on Human Reproduction

The Brazilian Society on Human Reproduction advises the applicants for the annual Campos da Paz Prize that original articles for consideration must be sent no later than November 30, 1980. The winner will receive a plaque, a diploma, and Cr\$15,000.

Papers in Portuguese, Spanish, English, and French published in scientific periodicals or presented in national or international medical meetings will be considered. If the paper has not been published, it can be presented in a maximum of 10 typewritten pages, double spaced, including illustrations and bibliography.

(three copies required). If not previously published, the prize-winning paper will be published in the journal *Reproduction*.

Articles should be sent to: Dr. Waldemar Diniz P. de Carvalho, President, Barzilian Society on Human Reproduction, Rua Ximbó, 165 CEP 04108, São Paulo, Brazil.

#### Fourteenth Annual Convention of the Association for Advancement of Behavior Therapy

The Association for Advancement of Behavior Therapy will hold its Fourteenth Annual Convention, November 20-23, 1980, at the New York Hilton, New York, New York.

For information write to: Steven C. Hayes, Ph.D., Program Chairperson, Association for Advancement of Behavior Therapy, 420 Lexington Ave., New York, New York 10170.

#### **Current Perspectives in Reproductive Health**

The Division of Reproductive Endocrinology Nursing, Department of Gynecology and Obstetrics, The Johns Hopkins Medical Institutions, will offer a continuing education conference, entitled "Current Perspectives in Reproductive Health," to be held November 10-11, 1980, in Baltimore, Maryland.

For further information contact: Program Coordinator, The Johns Hopkins University, Turner Auditorium, 720 Rutland Ave., Baltimore, Maryland 21205.

#### Second Biennial Clinical Conference of the National Perinatal Association

The National Perinatal Association's Second Biennial Clinical Conference will be held November 2-5, 1980, in Atlanta, Georgia.

For more information contact: Deborah Bulger, The Perinatal Center, Sutter Community Hospitals, 52nd and F Streets, Sacramento, California 95819.

#### First Brazilian Congress of Sexology

The First Brazilian Congress of Sexology will be held by the Brazilian Society of Sexology in Rio de Janeiro, Brazil, November 7 to 9, 1980.

For information write: Prof. Isaac Charam, President: Sociedade Brasileira de Sexologia, Rua Barata Ribeiro 418 apt. 111, Copacabana, Rio de Janeiro, Brazil.

#### Postgraduate Symposium in Spanish on Modern Management of Endocrinology, Infertility, and Contraception

The University of Texas Health Science Center at San Antonio will present a Postgraduate Symposium in Spanish on Modern Management of Endocrinology, Infertility and Contraception, March 26-28, 1981.

For information contact Program Director: Ricardo H. Asch, M.D., 7703 Floyd Curl Dr., San Antonio, Texas 78284.

#### International Symposium on Progesterone and Progestins

An International Symposium on Progesterone and Progestins will be held on May 7-9, 1981, in Paris, France (Organizing Committee: C. W. Bardin, United States; P. Mauvais-Jarvis, France; E. Milgrom, France). The official languages of the Symposium will be English and French.

Additional information regarding the Symposium and registration forms can be obtained from: Dr. P. Mauvais-Jarvis, Service d'Endocrinologie, Hopital Necker, 149, rue de Sevres, 75730 Paris Cedex 15, France.

#### Second Conference on the Control of the Onset of Puberty

This Conference will be held in Stresa, Italy, on September 15-18, 1981. It is sponsored by the University of California, San Francisco, the University of Geneva Medical School (Switzerland), the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and Serono Symposia.

For further information, please contact the Organizing Secretariat: Serono Symposia, Via Ravenna, 8, 00161 Rome, Italy.

#### Sixth Annual Obstetrics and Gynecology Review Course and Pathology Course

The University of Miami School of Medicine, Department of Obstetrics and Gynecology, will sponsor the Sixth Annual Obstetrics and Gynecology Review Course and Pathology Review which will be held October 17-23, 1980, at the Intercontinental Miami Hotel, 301 S. Bayshore Drive, Miami, Florida.

Information may be obtained from the Department of Obstetrics and Gynecology, University of Miami School of Medicine (R-116) P. O. Box 016960, Miami, Florida 33101.

#### CHARLES C THOMAS · PUBLISHER

New! THE SEXUAL VICTIMOLOGY OF YOUTH edited by LeRoy G. Schultz, West Virginia Univ., Morgantown. (21 Contributors) Recognition and treatment of the physical and psychological effects of incest, rape, child molestation, and other sexual traumata of children and adolescents are fully detailed in this text. Medical models drawn from emergency room cases and gynecology clinic records illustrate the various modes of presentation of sexual abuse and provide an indication of the types and number of cases appearing in the pediatric setting. Other topics include the child victim and the criminal justice system, the child sex industry, and sexual emancipation. '80, 432 pp., 1 il., 6 tables, \$19.75

New! FACULTY DEVELOPMENT THROUGH WORKSHOPS by Carole J. Bland, Univ. of Minnesota Medical School, Minneapolis. Foreword by Theodore J. Phillips. Practical guidelines, specific suggestions, and sample forms highlight this guide to planning, conducting, and evaluating faculty development workshops. Such organizational activities as selecting a coordinator and staff, assessing participants' needs, establishing goals and objectives, preparing a budget, outlining teaching strategies, planning evaluations, and selecting a site are sequentially listed and explained for the reader. '80, 232 pp., cloth-\$13.50, paper-\$9.75

New! THE ENERGY COUPLE: The New Sexuality by Douglas Q. Corey and Jeannette P. Maas, both of Savusavu, Fiji. '80, 160 pp., 42 il., \$9.95

FEMALE URINARY STRESS INCONTINENCE edited by Edward B. Cantor, Cedars-Sinai Medical Center, Los Angeles. Foreword by C. Paul Hodgkinson. (16 Contributors: This comprehensive text on female urinary stress incontinence covers the latest theoretical and practical aspects of neuroanatomy, physiology, and urodynamics. Chapters describe the supports of the urethra and the role of the pubourethral ligaments, analyze the anatomical defects involved in inadequate pelvic supports, and detail electronic diagnostic modalities. Also discussed are the utilization of the posterior pubourethral ligaments via a suprapubic approach, the detrusor dyssynergia syndrome, the electronic vaginal pessary, and the sling operations. '79, 360 pp., 175 il., 19 tables, \$30.25

BIRTH DEFECTS AND FETAL DEVELOPMENT: Endocrine and Metabolic Factors edited by Kamran S. Moghissi, Wayne State Univ., Detroit. (22 Contributors) '74, 352 pt., 94 il. (1 in color), 45 tables, \$31.00

THE PAP SMEAR: Life of George N. Papanicolaou by D. Erskine Carmichael, Univ. of Alabama, Birmingham. '73, 140 pp., 51 il., \$10.25

MATERNAL AND CHILD HEALTH PRACTICES: Problems, Resources and Methods of Delivery edited by Helen M. Wallace and Edwin M. Gold, both of Univ. of California, Berkeley, and Edward F. Lis, Univ of Illinois Medical Center, Chicago. (65 Contributors) Discussion includes identification and management of high risk pregnancy, maternal nutrition, genetic factors, perinatal mortality and morbidity, family planning, child health supervision, and other related topics. The history and development of maternal and child health services is also covered. '73, 1,400 pp., 49 il., 170 tables, \$47.50

New! COMMUNICATIONS IN A HEALTH CARI SETTING edited by Myron G. Eisenberg and Judith Fal coner, both of VA Medical Center, Cleveland, Ohio; and Lafaye C. Sutkin, VA Medical Center, Loma Linda, Cali fornia. This book demonstrates how the improvement of crucial communication patterns can help to achieve the goals of health care. It clarifies the definition of communication between individuals and groups connected with health care. Among the specific topics addressed are legal implications, the medical record, nonverbal messages and audio visual educational aids. '80, 288 pp., 11 il., 4 tables, \$19.7.

New! PRACTICAL CLINICAL CYTOLOGY by Virginia A. LiVolsi, Yale Univ. School of Medicine, New Haven, Connecticut. '80, 352 pp. (6 3/4 x 9 3/4), 97 il., 3 tables, \$32.50

New! SEXUAL COUNSELING FOR OSTOMATES A Resource Book for Health Care Professionals by Ellen A Shipes, Grady Memorial Hospital, and Sally T. Lehi Emory Univ., both of Atlanta. '80, 96 pp. (4 1/2 x 7), 59 il \$7.75, Lexotone

PRINCIPLES AND METHODS OF STERILIZATION IF HEALTH SCIENCES (2nd Ed., 6th Ptg.) by John J. Per kins. This volume covers automation, mechanical equipment, methods, techniques, and procedures related to al types of sterilization. Instructions for operating sterilizers proper methods of packaging supplies, types of termina sterilization for decontamination of articles, use of cultur tests and sterilizer controls, and problems of star dardization of sterilizing techniques are all detailed. '80, 58 pp. (6 3/4 x 9 3/4), 206 il., 33 tables, \$22.75

CLINICAL ATLAS OF GRAY SCALE ULTRASONOC RAPHY IN OBSTETRICS by Alan V. Cadkin and Marti N. Motew, both of Michael Reese Hospital and Medica Center, Chicago. Contribution by Rudy E. Sabbagha. Ove 700 high quality gray scale scans illuminate the clinica uses of real-time ultrasound and depict diagnostic finding and variations within normal and abnormal pregnancie. Among the many obstetrical conditions covered are th normal first trimester, multiple gestation, ectopic pregnancy, trophoblastic disease, and puerperium. Data o scanning techniques, gynecology, and the basic physics of ultrasound are included. '79, 384 pp. (8 1/2 x 11), 713 il., 1 tables, \$77.50

CHEMOSURGERY: Microscopically Controlled Surger for Skin Cancer by Frederic E. Mohs, Univ. of Wisconsi Medical School, Madison. '78, 400 pp. (6 3/4 x 9 3/4), 85 il., 59 tables, \$48.25

ENDOMETRIAL CARCINOMA AND ITS TREAT MENT: The Role of Irradiation, Extent of Surgery, an Approach to Chemotherapy edited by Laman A. Gray, Sr Univ. of Louisville, Louisville, Kentucky. (27 Contributors: The roles of radiotherapy, surgery, and chemotherapy is the treatment of endometrial carcinoma are examined, an reports from cancer centers and universities attesting to recent findings in the field are presented. Documented case of departures from the standard use of intrauterine radiur therapy before surgery are also included. '77, 240 pp. (63/x 9 3/4), 17 il., 138 tables, \$28.50

#### **Boston University School of Medicine Department of Obstetrics and Gynecology** announces

#### Second Annual Winter Symposium: **CLINICAL OBSTETRICS**

DATES: PLACE: February 8-13, 1981

The Mountain Inn, Killington, Vermont

TUITION FEE.

\$275.00 for M.D.'s, \$150.00 for residents & nurses; in-

cludes registration, handouts & welcome party

DESCRIPTION:

Five-day early morning and late afternoon didactic seminar covering current and practical management of common obstetrical problems. Two afternoon sessions will be devoted to presentation of registrants' problem

SKIING:

Killington 10:00 a.m. - 4:00 p.m. every day. Group

rates will be arranged.

**ACCREDITATION: AMA Category 1, ACOG** 

FACULTY:

David Acker, M.D., Boston City Hospital, Alan Altman, M.D., Boston Hospital for Women; Curtis Cetrulo, M.D., St. Margaret's Hospital; David Coulter, M.D., Boston City Hospital; and Jay Hendelman, M.D., Boston City Hospital

For further details and registration, contact:

Mary Hopkins

Boston University School of Medicine

Department of Continuing Medical Education

80 East Concord Street Boston, MA 02118 Phone 617-247-5602

#### THE UNIVERSITY OF TEXAS MEDICAL SCHOOL AT HOUSTON Department of Pathology & Laboratory Medicine Department of Obstetrics & Gynecology

and

THE UNIVERSITY OF TEXAS SYSTEM CANCER CENTER M.D. ANDERSON HOSPITAL AND TUMOR INSTITUTE Department of Gynecology

present

#### BASIC SCIENCE IN OBSTETRIC & GYNECOLOGIC PRACTICE

October 6-10, 1980 Houston, Texas

Distinguished Lecturer H. J. NORRIS, M.D.

For additional information, contact The University of Texas Medical School. Office of Continuing Education, PO Box 20708, Houston, Texas 77025, phone (713) 792-5346.

#### **PROFESSOR** AND CHAIRMAN DEPARTMENT OF OBSTETRICS & GYNECOLOGY

The University of Alberta, Faculty of Medicine, invites applications for the position of Chairman of the Department of Obstetrics and Gynecology of the University of Alberta and affiliated University of Alberta Hospital, starting July 1, 1981. Certification by the Royal College of Physicians and Surgeons of Canada (or equivalent) and eligibility for licensure in Alberta essential. This is a geographic full-time tenured academic appointment with responsibilities for the teaching, research and patient activities of a major medical school department. Applicants should have active research interests and demonstrated organization and administrative abilities. The University of Alberta is an equal opportunity employer.

Applications may be sent to Dr. D. F. Cameron, Dean, Faculty of Medicine. University of Alberta, Edmonton, Alberta, Canada.

#### **OBSTETRICIAN-GYNECOLOGIST**

**OBSTETRICIAN-GYNECOLOGIST**needed in historic Marshall, Michigan, located half-way between Ann Arbor and Kalamazoo, Michigan. Beautiful town with a 77 bed acute care hospital. City population of 7,500 and service area population of 22,000. Admitting staff includes: four (4) Family Practice Specialists, five (5) General Practitioners, two (2) General Surgeons and one (1) Internist. Willing to negotiate to attract a high caliber physician.

#### Contact:

Rob Covert, Administrator, or Philip Glotfelty, M.D., Chief of Staff Oaklawn Hospital 200 North Madison Marshall, Michigan, 49068. Or phone 616-781-4271, extension 201

#### MATERNAL-FETAL MEDICINE— JULY 1, 1981

Maternal-Fetal Medicine full-time faculty position in the Department of Obstetrics and Gynecology, Medical College of Virginia, Virginia Commonwealth University. Require Board certification in Obstetrics and Gynecology or its equivalent, and certification or eligibility in Maternal-Fetal Medicine or its equivalent. Responsibilities include undergraduate and graduate medical teaching, patient care, and clinical or laboratory research. Those interested should send their c.v. by January 1, 1981 to:

Leo J. Dunn, M.D. Professor and Chairman Department of OB/GYN Medical College of Virginia Richmond, Virginia 23298

M.C.V. IS AN EQUAL OPPORTUNITY EMPLOYER

#### PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in these specially designed library file cases. Designed to keep your journal copies near at hand in your office, library, or home.

Your case is heavy bookbinder's board in rich red Kivar cover. Files are scuff-resistant and washable.

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding.

Files are reasonably priced—only \$4.95 each, postpaid (3 for \$14., 6 for \$24.). Add \$1.00 postage per case for orders outside U. S. Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

Jesse Jones Box Corporation (est. 1843) P. Ö. Box 5120 Philadelphia, Pa. 19141

Please send me, postpaid \_\_\_\_\_library cases for AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY at \$4.95 each (3/\$14., 6/\$24.)

	NEW SIZE (8¼"					1077
1	OLD SIZE (7¼"	× 10%	copies	prior	10	19/5
	(2 cases/vear)					

Name			
City	State	Zip	

#### Perinatologist

Perinatologist—a position in Maternal/ Fetal Medicine is available at Texas Tech University Regional Academic Health Center in El Paso, Texas. This is a full time faculty position for Board eligible or certified practitioner. Excellent opportunity for active clinical service for direct patient care, resident and medical student teaching and research. Excellent salary in accordance with experience for appropriate individual. Growing fringe benefits program. Interested persons contact Billy Reeves, M.D. at 4800 Alberta Street, El Paso, Texas 79905 or M. Wayne Heine, M.D., TTUHSC, Department of Obstetrics-Gynecology, Lubbock, Texas 79430.

## Gynecologic Oncologist

Gynecologic Oncologist—Full time faculty position at the newly constructed cancer center associated with the Texas Tech Regional Academic Health Center in Amarillo, Texas. Excellent clinical opportunity for patient clinical service, teaching and research. Excellent salary in accordance with experience. Growing fringe benefits program. Interested persons contact Roger Perry, M.D. at 1400 Wallace Avenue, Amarillo, Texas 79106 (Phone: 806-355-8961) or M. Wayne Heine, M.D., TTUHSC, Department of Obstetrics/Gynecology, Lubbock, Texas 79430.

#### INDEX TO ADVERTISERS

Ayerst Laboratories	National Institutes of Health
Premarin 14, 15, 16	Genetics Fellowship 30
Baystate Medical Center	Oaklawn Hospital
Opportunity Available Third Cover	Opportunity Available 38
Boston University School of Medicine	Parke-Davis Division of Warner-Lambert Co.
Postgraduate Course 38	Loestrin 10. 11. 12
	Tabron 20
Brigham Medical Associates, Inc.	
Opportunity Available 34	Prime Health
	Opportunity Available 34
Davis Manager 1 IV and a l	
Bryan Memorial Hospital Opportunity Available Third Cover	Purdue Frederick Company, The
oppnumy nounce Innu dover	Senokot-S8
Burroughs Wellcome Co.	
Empirin c Codeine4	Sandoz
	Parlodel 25, 26, 27
Dorsey Laboratories	
Bellergal-S Third Cover, Fourth Cover	Syntex
,	Norinyl Second Cover, 1, 2
Health Care Plan	
Opportunity Available 34	Texas Tech University School of Medicine
	Opportunities Available 39
Hospital Corporation of America	
Opportunity Available 35	Thomas, Charles C.  Books 37
	Books
Ives Laboratories Inc.	The constant of Albania
Synalgos-DC36	University of Alberta Opportunity Available 38
	Opportunity Houseaute 50
Kaiser/Permanente Medical Center	University of Kansas School of Medicine-Wichita, The
Opportunities Available 30	Course 35
1	•
Life-Tech Instruments, Inc.	University of Tennessee, The
Urodynamic Instrumentation 33	Opportunity Available 35
	•
Louisiana State University Medical Center	University of Texas, The
Opportunity Available 34	Course 38
	•
Medical College of Virginia	Welch Allyn, Inc.
Opportunity Available 39	Halogen Exam Lite 18
	•
Menley & James Laboratories	Wyeth Laboratories
Feosol 3	Ovral 22, 23, 24
Merck, Sharp & Dohme	Zeiss, Inc., Carl
.Urecholine 31, 32	Operation Microscope 6

#### MATERNAL — FETAL MEDICINE

The Department of Obstetrics and Gynecology of the Baystate Medical Center in Springfield, Massachusetts, is seeking a full time Director for its Perinatal program. There are 5,000 in-house deliveries as well as 5.000 deliveries in 7 affiliated hospitals for this Perinatal system. The Department is affiliated with both Tufts and the University of Massachusetts Schools of Medicine. The Department has 40 community based Obstetricians-Gynecologists, 16 residents, and 4 additional full time faculty. The candidate must be board eligible in Maternal-Fetal Medicine, Salary and academic rank are commensurate with training and experience. Those interested please send CV to: Laurence E. Lundy. M.D., Chairman, Department of OB-GYN. Baystate Medical Center, 759 Chestnut Street, Springfield, Massachusetts 01107.

An Equal Opportunity Employer M/F/H

#### OB/GYN PHYSICIAN NEEDED

Bryan Memorial Hospital, Durant, OK, is seeking a trained OB/GYN Physician. The community is located 8 miles from beautiful Lake Texoma, 85 miles from Dallas, and 125 miles from Oklahoma City. Ideal location. Population 14,000. Catchment area 30,000. Home of Southeastern Oklahoma State University. Hospital is a J.C.A.H. 80 bed facility with very modern O.R., I.C.U., Labor/Delivery areas and other Ancillary Facilities. Present active staff includes 1 OB/GYN, 1 Pediatrician, 2 Surgeons, 4 G.P., 3 Cardiologists, 1 Radiologist. Urology, Pathology, Neurology services are also readily available. Clinic space available. Hospital and Chamber of Commerce is sponsoring a generous guarantee.

Please send C.V. to: Administrator, Bryan Memorial Hospital Durant, OK 74701 Telephone (405) 924-3080

#### BELLERGAL-STARLETS

Composition: Each Bellergal-S Tablet contains: phenobarbital, USP, central sedative (Warning: May be habit forming), 40.0 mg; Gynergen (ergotamine tartrate, USP) sympathetic inhibitor, 0.6 mg; Bellafoline (levorotatory alkaloids of belladonna, as malates) parasympathetic inhibitor, 0.2 mg.

Properties and Therapeutics: Based on the concept that functional disorders frequently involve hyperactivity of both the sympathetic and parasympathetic nervous systems, the ingredients in Bellergal are combined to provide a balanced preparation designed to correct imbalance of the autonomic nervous system. The integrated action of Bellergal is effected through the combined administration of ergotamine and the levorotatory alkaloids of belladonna, specific inhibitors of the sympathetic and parasympathetic respectively, reinforced by the synergistic action of phenobarbital in dampening the cortical centers.

**Indications:** Bellergal is employed in the management of disorders characterized by nervous tension and exaggerated autonomic response:

<u>Menopausal disorders</u> with hot flashes, sweats, restlessness and insomnia.

<u>Cardiovascular disorders</u> with palpitation, tachycardia, chest oppression and vasomotor disturbances.

<u>Gastrointestinal disorders</u> with hypermotility, hypersecretion, "nervous stomach," and alternately diarrhea and constipation.

Genitourinary-uterine cramps, etc.

Premenstrual tension.

Interval treatment of <u>recurrent</u>, <u>throbbing</u> <u>headache</u>.

Contraindications: Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis, third trimester of pregnancy and glaucoma. Hypersensitivity to any of the components.

Precautions: Even though the ergotamine tartrate content of this product is extremely low and untoward effects have been rare and insignificant, caution should be exercised if large or prolonged dosage is contemplated, and physicians should be alert to possible peripheral vascular complications in patients highly sensitive to ergot. Due to presence of a barbiturate, may be habit forming.

**Side Effects:** Blurred vision, dry mouth, flushing, drowsiness occur rarely.

**Dosage:** Bellergal-S Tablets: One in the morning and one in the evening.

**How Supplied:** Bellergal-S Tablets (compressed, scored tablets of tricolored pattern: dark green, orange and light lemon yellow) in bottles of 100.

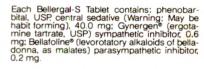
Dorey
LABORATORIES
Division of Sandoz, Inc.
LINCOLN, NEBRASKA 6850

# NONHORMONAL therapy for menopausal vasomotor instability is receiving renewed attention.



# BELLERGAL-S

## TABLETS

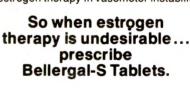




Long clinical experience has established the effectiveness of Bellergal-S Tablets in managing menopausal disorders characterized by exaggerated autonomic response—hot flashes, sweats, restlessness, and insomnia.

Because Bellergal-S reduces autonomic nervous system activity, symptoms of vasomotor instability are eliminated or significantly reduced. Bellergal-S does not contain estrogen in any form. That's one reason why it is receiving renewed attention from physicians who wish to avoid the potential complications of estrogen therapy in vasomotor instability.





Please see prescribing information on an adjoining page.

© 1979 Dorsey Laboratories/Division of Sandoz, Inc.

September 15, 1980 volume 138, number 2

# American Journal OF OBSTETRICS AND GYNECOLOGY

Copyright @ 1980 by The C. V. Mosby Company

Editor in Chief
JOHN I. BREWER

Editors

FREDERICK P. ZUSPAN · E. J. QUILLIGAN

Associate Editor

Emeritus Editors

HOWARD C. TAYLOR, JR. · ALLAN C. BARNES

#### Official Publication

AMERICAN GYNECOLOGICAL SOCIETY

AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA
SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
PACIFIC COAST OBSTETRICAL AND GYNECOLOGICAL SOCIETY
AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY
SOCIETY FOR GYNECOLOGIC INVESTIGATION



Published by

THE C. V. MOSBY COMPANY St. Louis, Missouri 63141



ISSN 0002-9378

#### Four kinds of contraceptive priorities...



- 1. She wants convenience.
- 2. She wants nonhormonal contraception.
- 3. She smokes.
- 4. She is over 35.

## Cu→/ Tatum (intrauterine copper contraceptives)

- Answer their contraceptive priorities...
- 1. For the contemporary woman who wants free-\_dom from rigid schedules, the copper IUD is a logical choice because of its inherent convenience.
- 2. For the new mother who wants to space her family...the copper IUD has no effect on lactation. Its efficacy rate is almost as high as that of the Pill.



cially opportune time to insert a Cu-7 or Tatum-T, providing involution has occurred.

- 3. For the woman—of any age—who smokes, the copper IUD produces no problems in association with smoking.
- 4. For the woman who has passed the Pill years, but who still wants highly effective and reversible contraception, the copper IUDs are a logical choice.

Intrauterine contraception is not appropriate for all women. See complete prescribing information prior to use. Please see next page for a brief summary of product information. •

#### Cu-7/ Tatum-T

#### (intrauterine copper contraceptives)

**Description:** The Cu-7 has coiled around the vertical limb 89 mg. of copper wire providing approximately 200 mm² of exposed copper surface area. The Tatum-T has coiled around the vertical limb 120 mg. of copper wire providing approximately 210 mm² of exposed copper

Contraindications: Not to be inserted when any of the following conditions exist: pregnancy or suspicion of pregnancy; abnormalities of the uterus resulting in distortion of the uterine cavity; acute pelvic inflammatory disease or history of repeated pelvic inflammatory disease; postpartum endometritis or infected abortion in the past three months; known or suspected uterine or cervical disease such as hyperplasia or carcinoma including unresolved, abnormal "Pap" smear; vaginal bleeding of unknown etiology; untreated acute cervicitis until infection is controlled, diagnosed Wilson's disease; known or suspected allergy to copper; previous ectopic pregnancy; significant anemia; and valvular heart disease, leukemia, or use of chronic corticosteroid therapy

#### Warnings

1. Pregnancy: (a) Long-term effects. The long-term effects on the offspring of the presence of

copper in the uterus when pregnancy occurs are unknown.

(b) Septic abortion. Reports have indicated an increased incidence of septic abortion associated in some instances with septicemia, septic shock and death in patients becoming pregnant with an IUD in place. Most of these reports have been associated with the midtrimester of pregnancy. In some cases, the initial symptoms have been insidious and not easily recognized. If pregnancy should occur with a Cu-7 or Tatum-T in situ, the IUD should be removed if the thread is visible or, if removal proves to be or would be difficult, interruption of the pregnancy should be considered and offered to the patient as an option, bearing in mind

the pregnancy should be considered and ordered to the patient as an option, bearing in mind that the risks associated with an elective abortion increase with gestational age.

(c) Continuation of pregnancy. If the patient chooses to continue the pregnancy and the Cu-7 or Tatum-T remains in situ, she must be warned of increased risk of spontaneous abortion and increased risk of sepsis, including death. The patient must be closely observed and advised to report immediately all abnormal symptoms, such as flu-like syndrome, fever, abdominal cramping and pain, bleeding, or vaginal discharge, because generalized expertence of certificing may be inseltique.

symptoms of septicemia may be insidious

2. Ectopic pregnancy: (a) Pregnancy which occurs with an IUD in situ is more likely to be ectopic than pregnancy occurring without an IUD. Therefore, patients who become pregnant while using a Cu-7 or Tatum-T should be carefully evaluated for the possibility of ectopic

(b) Special attention should be directed to patients with delayed menses, slight metrorrhagia and/or unilateral pelvic pain, and to those patients who wish to interrupt a pregnancy occurring in the presence of a Cu-7 or Tatum-T, to determine whether ectopic

pregnancy has occurred

Pelvic infection: An increased risk of pelvic inflammatory disease associated with the use of IUDs has been reported. While unconfirmed, this risk appears to be greatest for young women who are nulliparous and/or who have multiple sexual partners. Salpingitis can result in tubal damage and occlusion, thereby threatening future fertility. Therefore, it is recommended that patients be taught to look for symptoms of pelvic inflammatory disease. The decision to use an IUD in a particular case must be made by the physician and patient with

consideration of a possible deleterious effect on future fertility.

Pelvic infection may occur with a Cu-7 or Tatum-T in situ and at times result in the development of tubo-ovarian abscesses or general peritonitis. The symptoms of pelvic infection include: new development of menstrual disorders (prolonged or heavy bleeding) abnormal vaginal discharge, abdominal or pelvic pain, dyspareunia, fever. The symptoms are especially significant if they occur following the first few cycles after insertion. Appropriate aerobic and anaerobic bacteriologic studies should be done and antibiotic therapy initiated promptly. If the infection does not show marked clinical improvement within 24 to 48 hours, the Cu-7 or Tatum-T should be removed and continuing treatment reassessed on the basis of results of culture and sensitivity tests

- 4. Embedment: Partial penetration or lodging of the Cu-7 or Tatum-T in the endometrium or myometrium can result in difficult removal. This may occur more frequently in smaller uten. See removal instructions
- 5. <u>Perforation</u>: Partial or total perforation of the uterine wall or cervix may occur, usually during insertions into patients sooner than two months after abortion or delivery, or in uterine cavities too small. The possibility of perforation must be kept in mind during insertion and at the time of any subsequent examination. If perforation occurs, laparotomy or laparoscopy should be performed as soon as medically feasible and the Cu-7 or Tatum-1 removed. Abdominal adhesions, intestinal penetration, intestinal obstruction, and local inflammatory reaction with abscess formation and erosion of adjacent viscera may result if the Cu-7 or Tatum-T is left in the peritoneal cavity
- 6. <u>Medical diathermy</u>: The use of medical diathermy (short-wave and microwave) in a patient with a metal-containing IUD may cause heat injury to surrounding tissue. Therefore, medical diathermy to the abdominal and sacral areas should not be used on patients using a Cu-7 or
- 7. Effects of copper: Additional amounts of copper available to the body from the Cu-7 or Tatum-T may precipitate symptoms in women with undiagnosed Wilson's disease. The incidence of Wilson's disease is 1 in 200,000.

- Patient counseling. Prior to insertion the physician, nurse, or other trained health professional must provide the patient with the Patient Brochure. The patient should be given the opportunity to read the brochure and discuss fully any questions she may have concerning the Cu-7 or Tatum-T as well as other methods of contraception
- Patient evaluation and clinical considerations. (a) A complete medical history should be obtained to determine conditions that might influence the selection of an IUD. A physical examination should include a pelvic examination, "Pap" smear, gonorrhea culture and, if indicated, appropriate tests for other forms of venereal disease. The physician should determine that the patient is not pregnant.

(b) The uterus should be carefully sounded prior to insertion to determine the degree of patency of the endocervical canal and internal os, and the direction and depth of the uterine

cavity. Exercise care to avoid perforation with the sound. DO NOT USE THE INSERTION INSTRUMENT AS A SOUND. In occasional cases, severe cervical stenosis may be

INSTRUMENT AS A SUUND. In occasional cases, severe cervical stenosis may be encountered. Do not use excessive force to overcome this resistance.

(c) The uterus usually sounds to a depth of 6 to 8 cm. Insertion into a uterine cavity measuring less than 6.5 cm. by sounding may increase the incidence of pain, bleeding, partial or complete expulsion, perforation, and possibly pregnancy.

(d) To reduce the possibility of insertion in the presence of existing undetermined pregnancy, the optimal time for insertion is the latter part of the menstrual flow or one or two days thereafter. The City? or Tatum I should not be inserted not agriculture or not abortion until days thereafter. The Cu-7 or Tatum-T should not be inserted post partum or post abortion until involution of the uterus is complete. The incidence of perforation and expulsion is greater if involution is not complete.

It is, however, necessary to place the Cu-7 or Tatum-Tas high as possible within the uterine cavity to help avoid partial or complete expulsion that could result in pregnancy.

Physicians are cautioned that it is imperative for them to become thoroughly familiar with

replacement of the Cu-7 or Tatum-T.

(e) IUDs should be used with caution in those patients who have anemia or a history of menorrhagia or hypermenorrhea. Patients experiencing menorrhagia and/or metrorrhagia following IUD insertion may be at risk for the development of hypochromic microcytic anemia. Also, IUDs should be used with caution in patients receiving anticoagulants or

having a coagulopathy.

(f) Syncope, bradycardia or other neurovascular episodes may occur during insertion or removal of IUDs, especially in patients with a previous disposition to these conditions.

(g) Patients with valvular or congenital heart disease are more prone to develop subacute bacterial endocarditis than patients who do not have such disease. Use of an IUD in these patients may represent a potential source of septic emboli.

(h) Use of an IUD in patients with acute cervicitis should be postponed until proper

treatment has cleared up the infection.

- (i) Since the Cu-7 or Tatum-T may be partially or completely expelled, patients should be reexamined and evaluated shortly after the first postinsertion menses, but definitely within three months after insertion. Thereafter annual examination with appropriate medical and laboratory evaluation should be carried out. The Cu-7 or Tatum-T should be replaced every three years
- (j) The patient should be told that some bleeding or cramping may occur during the first few weeks after insertion, but if these symptoms continue or are severe she should report them to her physician. She should be instructed on how to check after each menstrual period to make certain that the thread still protrudes from the cervix and cautioned that there is no contraceptive protection if the Cu-7 or Tatum-T has been expelled. She should also be cautioned not to dislodge the Cu-7 or Tatum-T by pulling on the thread. If a partial expension occurs, removal is indicated and a new Cu-7 or Tatum-T may be inserted. The patient should be told to return within three years for removal of the Cu-7 or Tatum-T and for replacement if

(k) A copper-induced urticarial allergic skin reaction may develop in women using a copper-containing IUD. If symptoms of such an allergic response occur, the patient should be

- instructed to tell the consulting physician that a copper-containing device is being used.
  (I) The Cu-7 or Tatum-T should be removed for the following medical reasons; menorrhagia and/or metrorrhagia producing significant anemia; uncontrolled pelvic infection; intractable pain often aggravated by intercourse, dyspareunia; pregnancy, if the thread is visible; endometrial or cervical malignancy; uterine or cervical perforation; or any indication of partial
- (m) If the retrieval thread cannot be seen it may have retracted into the uterus or have been broken off, or the Cu-7 or Tatum-T may have been expelled. Localization usually can be made by feeling with a probe; if not, x-ray or sonography can be used. When the physician elects to recover a Cu-7 or Tatum-T with the thread not visible, the removal instructions should be
- (n) If any patient with a Cu-7 or Tatum-T suddenly develops overt clinical hepatitis or abnormal liver function tests, appropriate diagnostic procedures should be initiated

Adverse Reactions: Perforations of uterus and cervix have occurred. Perforation into the abdomen has been followed by abdominal adhesions, intestinal penetration, intestinal obstruction, local inflammatory reaction with abscess formation and erosion of adjacent viscera. Pregnancy has occurred with the Cu-7 or Tatum-T in situ and when either has been partially or complétely expelled.

The incidence of spontaneous abortion, when conception occurs with intrauterine devices

in situ, appears to be increased over that in unprotected women. Insertion cramping, usually of no more than a few seconds' duration, may occur, however, some women may experience residual cramping for several hours or even days. Intermenstrual spotting or bleeding or

residual cramping for several nours or even days, intermenstrual spotting or pleeding or prolonged or increased menstrual flow may occur. Pelvic infection including salpingitis with tubal damage or occlusion has been reported. This may result in future infertility. Complete or partial expulsion of the Cu-7 or Tatum-T may sometimes occur, particularly in those patients with uteri measuring less than 6.5 cm. by sounding. Urticarial allergic skin reaction may occur. The following complaints have also been reported with IUDs although their relation to the Cu-7 or Tatum-T has not been established: amenorrhea or delayed menses, backaches, cervical erosion, cystic masses in the pelvis, vaginitis, leg pain or soreness, weight loss or gain, nervousness, dyspareunia cystitis, endometritis, septic abortion, septicemia, leukorrhea, ectopic pregnancy, difficult removal, uterine embedment, anemia, pain, neurovascular episodes including bradycardia and syncope secondary to insertion, dysmenorrhea, and fragmentation of the IUD.

Clinical Efficacy: In clinical trials, use effectiveness was determined as follows for parous and nulliparous women, as tabulated by the life table method. (Rates are expressed as cumulative events per 100 women through 12, 24, and 36 months of use.)

Cu-7 experience encompasses 387,131 women-months of use, including 12 months for 1,1517 women, 24 months for 7,895, and 36 months for 3,661.

Tatum-T experience encompasses 236.060 woman-months of use in the United States and Canada, including 12 months for 8,232 women, 24 months for 4,247, and 36 months for 1,408.

Cumulative pregnancy rates were:

						onths
Cu-7	1.9	1.7	2.9	2.6	3.4	ulliparous 3.4
Tatum-T	3.0	2.1	4.9	4.5	6.0	5.8 -
Please see comple	te product labeli	ng for add	itional infor	mation in	cluding in	sertion and

removal instructions







#### RhoGAM Rho(D) Immune Globulin (Human)

Indications: RhoGAM Rh $_{\rm o}$  (D) Immune Globulin (Human) is used to prevent formation of active anti-Rh $_{\rm o}$  (D) antibody in an Rh $_{\rm o}$  (D) negative, D $^{\rm o}$  negative individual into whose bloodstream Rh $_{\rm o}$  (D) positive or D $^{\rm o}$  positive blood has entered. Such an occurrence might result from full term or early termination of an Rh incompatible pregnancy, or from an Rh incompatible transfusion.

**Dosage:** One vial of RhoGAM will completely suppress immunity to 15 ml of Rh positive red blood cells (packed cells, not whole blood). In deciding the dose of RhoGAM which is to be administered to an individual, the volume of Rh positive blood which entered the person's bloodstream is to be determined, from which the dose of RhoGAM can be calculated. In the usual full-term delivery, a single dose (one vial) of RhoGAM will be adequate to suppress immunity to the Rh<sub>o</sub>(D) antigen. However, in the case of a large feto-maternal hemorrhage

or an Rh incompatible transfusion accident, more than one dose may be indicated.

 $\begin{array}{l} \textbf{Product Description:} \ RhoGAM \ is \ a \ sterile\\ concentrated \ solution \ of \ specific \ immunoglobulin \ (lgG)\\ containing \ anti-Rh_o \ (D) \ fractionated \ from \ carefully\\ screened \ human \ plasma \ by \ a \ cold \ alcohol \ method. \end{array}$ 

**Action:** With an injection of passive  $Rh_o(D)$  antibody (RhoGAM) to the postpartum mother, a postmiscarriage/abortion woman, or to the recipient of a transfusion accident, the person's antibody response to the foreign  $Rh_o(D)$  positive cells is suppressed.

Cautions: Reactions of Rh<sub>o</sub> (D) negative individuals given Rh<sub>o</sub> (D) Immune Globulin (Human) are infrequent, of a mild nature and mostly confined to the area of injection. An occasional patient may react more strongly, both locally and generally. A slight elevation of temperature has been noted in a small number of postpartum women.

Fever, myalgia, lethargy, increased bilirubin levels and/or splenomegaly have been infrequently observed in individuals following a multi-dose regimen after Rh mismatched transfusions. Systemic reactions are rare and sensitization due to repeated injections of immune globulins is unusual. Immune Serum Globulin (Human) has not been reported to transmit hepatitis.

RhoGAM is to be given to the recipient in a transfusion accident or the postpartum mother or postmiscarriage woman, only. It must not be given to the infant.

 $\textbf{Contraindications:} \ Rh_o\left(D\right) Immune \ Globulin \left(Human\right) \\ should \textit{not} \ be \ administered \ to:$ 

- 1. An Rh<sub>o</sub> (D) positive or D<sup>u</sup> positive individual.
- 2. An  $Rh_{\sigma}(D)$  negative patient who has inadvertently received an  $Rh_{\sigma}(D)$  positive blood transfusion within three months of delivery.
- 3. A patient previously immunized to the  $Rh_{\circ}\left(D\right)$  blood factor.

**Supplied:** In vials containing a single dose of RhoGAM. Store at 2° to 8° C. Do not freeze.

NOTE: For complete prescribing information, see

# Twenty thousand infants owe their lives to Rho(D) Immune Globulin (Human) and to you.

Since RhoGAM was first administered, over a decade ago, an estimated one hundred thousand sensitizations have been avoided, and twenty thousand fetal deaths from Rh hemolytic disease have been prevented.<sup>1</sup>

This outstanding achievement by the medical community is the direct result of the knowledge-able use of the proven prevention.

While there is still room for improvement...the record to date deserves recognition.

As the company that provides RhoGAM, and MICRhoGAM\* Rho(D) Immune Globulin (Human), Micro-Dose, Ortho Diagnostics shares in your continuing commitment to the eradication of Rh hemolytic disease.

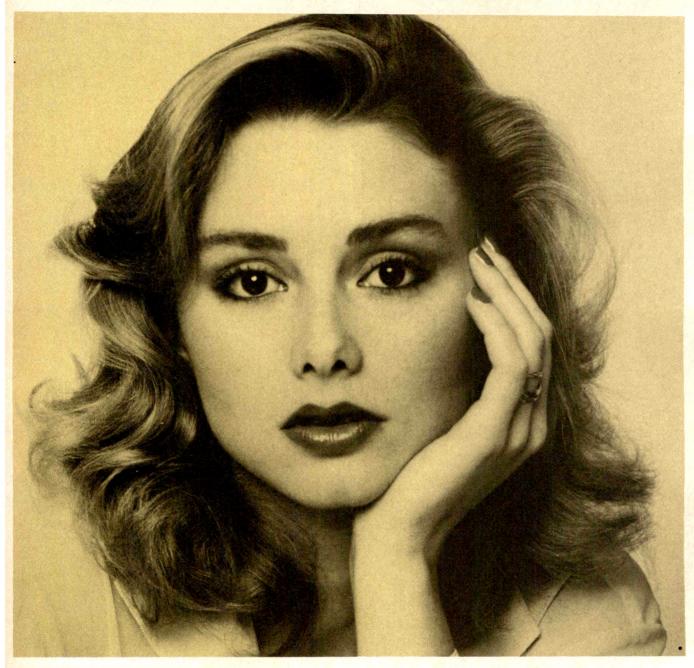
We have acted on our commitment with products and services to spread knowledge and understanding of the need to protect. We have sponsored continuing research and education with international symposia, books, pamphlets and films. We have helped design a record-keeping system to improve utilization, and have provided support to the medical profession with the RhoGAM Protection Policy.

We are doing all we can to help you help every patient at risk. There is still more to be done, and together we will find the way!

RhoGAM...the proven product.

<sup>1</sup>Center for Disease Control: Rh Hemolytic Disease: Surveillance, August 1976, Revision, DHEW Publication No. (CDC) 75-8310, Atlanta, 1976.





#### Prescribe KOROMEX®...for her comfort and confidence.

Many women today are asking you about changing their contraceptive method, and with good reason. Contraceptives are supposed to promote confidence. You and your patients realize that pills and IUD's frequently lead to

unpleasant side effects.

But KOROMEX products offer a gentle, effective barrier contraceptive. When you prescribe KOROMEX (coil spring) or the KOROFLEX farcing spring) vaginal

diaphragms, and KOROMEX spermicidal creams, jellies, or foam, your patient benefits from an increasingly accepted method of contraception.

Unlike other jellies and creams, KOROMEX doesn't have a strong perfume or medicinal odor. KOROMEX"-A Jelly

odor. KOROMEX"-A Jelly and KOROMEX Foam can both be used alone for effective protection.

Fifty years of experience stand behind this non-hormonal birth control method.



While no contraceptive provides 100% protection. Koromex products, when properly used, effectively aid in the prevention of pregnancy.

#### American Journal of Obstetrics and Gynecology

**Contents** 

Copyright © 1980 by The C. V. Mosby Company

#### September 15

1980

#### Clinical opinion

#### Technical progress in pelvic surgery via operative laparoscopy

121

K. Semm and L. Mettler Kiel, Germany

#### Gynecology

#### The treatment of endometriosis at laparoscopy for infertility

128

Joan M. Sulewski, M.D., Frederick D. Curcio, M.D., Carl Bronitsky, M.D., and Vincent G. Stenger, M.D.

Hershey, Pennsylvania

(Contents continued on page 7)

Vol. 138, No. 2, September 15, 1980. The American Journal of Obstetrics and Gynecology is published semimonthly by The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141. POSTMASTER: Send address changes to above address.

1980 Annual subscription rates	U.S.A.	Foreign countries (surface mail) All regions	Region 1	Foreign countries (airmail)* Region 2	Region 3
Institutional†	\$52.50	\$72.50	\$101.45	\$132.65	\$163.85
Individual‡	\$35.50	\$55.50	\$ 84.45	\$115.65	\$146.85
Student, resident‡	\$28.40	\$48.40	\$ 77.35	\$108.55	\$139.75

Single copies are \$4.50 postpaid. Remittances should be made by check, draft, or post office or express money order,

payable to this JOURNAL.
\*Airmail breakdown—Domestic: First-class and Priority rates for the U.S. and possessions are available upon request. Region 1: Central America, islands, and mainland colonies of European countries in The Americas. Region 2: South America, Europe, Egypt, Africa (bordering the Mediterranean). Region 3: Asia, Australasia, Africa (other than Mediterranean), Middle East, Far East, The Pacific, U.S.S.R. (and constituent Republics).

†Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics; city, county, state, provincial, and national government bureaus and departments; and all commercial and private institutions and organizations.

‡Personal subscriptions and all student-rate subscriptions must be in the names of, billed to, and paid by individuals. All student-rate requests must indicate training status and name of institution. Subscriptions may begin at any time.

Second-class postage paid at St. Louis, Missouri, and additional mailing offices. Printed in the U.S.A. Copyright © 1980 by The C. V. Mosby Company.

# Clinical ANEW BOOK! Synecologic Incology

By Philip J. DiSaia, M.D. and William T. Creasman, M.D.

This new book provides valuable guidelines for the diagnosis, treatment, and clinical management of common gynecologic malignancies. Its concise yet thorough coverage makes it a convenient reference source for the busy practitioner or for residents studying for the OB/GYN Boards. Key features include:

- Drs. Disaia and Creasman discuss current management methods as well as their own proven and preferred treatment suggestions
- chapters present information on etiology, pathological evaluation, diagnosis, clinical presentation, treatment and management, and recurrent disease
- discussions emphasize individualization

of patient management

- chapters of special interest:
   cancer in pregnancy
   breast disease
   general aspects of tumor immunology
   adrenocarcinoma of the endometrium
- a glossary of terms for tumor immunology and an appendix containing information on F.I.G.O. staging and basic aspects of gynecologic radiotherapy are included
- a wealth of illustrations, tables, and charts depict clinical principles

Order your on-approval copy today and examine it for 30 days with no obligation!
October, 1980. Approx. 464 pages, 178 illustrations. About \$29.50.

# You'll want this book you hand.

TIMES MIRROR

THE C. V. MOSBY COMPANY 11830 WESTLINE INDUSTRIAL DRIVE ST. LOUIS, MISSOURI 63141

To order your 30-day on-approval copies, CALL US!
Dial toll-free (800) 325-4177, ext. 10. In Missouri,
-call collect (314) 872-8370, ext. 10 during our regular
business hours.

AMS232

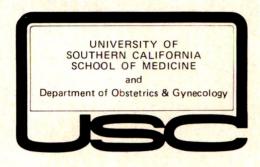
MasterCard, VISA, or C.O.D. accepted.

Price subject to change.

Add sales tax if applicable.

#### Contents continued from page 5

Com		
XY gonad	al dysgenesis in three siblings	133
	sey, M.D., R. Satterfield, M.D., R. J. Jorgenson, D.D.S., C. F. Salinas, D.D.S.,	
	r, M.S., R. S. Mathur, Ph.D., and H. O. Williamson, M.D.	
	South Carolina	
The role	of adjuvant therapy in Stage I ovarian cancer	139
Myroslaw	M. Hreshchyshyn, M.D., Robert C. Park, M.D., Colonel, MC, USA,	
John A. B	essing, Ph.D., Henry J. Norris, M.D., David Levy, M.D., Leo D. Lagasse, M.D.,	
	n T. Creasman, M.D.	
Philadelph	a, Pennsylvania	
Progress	ve histobiologic alterations in the development of vulvar cancer	146
Joseph Bu	scema, B.A., and J. Donald Woodruff, M.D.	
Baltimore,	Maryland	
Carbohyo	Irate metabolism with three months of low-estrogen contraceptive use	151
W. N. Spe	llacy, M.D., W. C. Buhi, M.S., and S. A. Birk, R.N., B.S.	
	Florida	
Gainesville	, rioria	
Gainesville		156
Gainesville The effect	t of copper on spermatozoal motility and viability evaluated objectively	156
The effect with the	t of copper on spermatozoal motility and viability evaluated objectively	156
The effect with the	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.	156
The effect with the a	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.	156
The effect with the a Amnon M Haifa, Isra	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.	156
The effect with the and Amnon Mind Haifa, Israel	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.	156
The effect with the Amnon M Haifa, Isra	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.	156
The effect with the Amnon M Haifa, Isra	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.  etrics  colume expansion in the treatment of pre-eclampsia	
The effect with the attack Amnon M Haifa, Israel  Obsteen Plasma with Narinder M	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.	
Charleston	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D. at least of the column expansion in the treatment of pre-eclampsia J. Sehgal, M.D., and John R. Hitt, M.D. at least virginia	165
Charleston  Gainesville  The effect with the attention of the control  Amnon M  Haifa, Isra  Obsta  Plasma v  Narinder M  Charleston  Genetic attention	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.  Tel  Olume expansion in the treatment of pre-eclampsia  N. Sehgal, M.D., and John R. Hitt, M.D.  N. West Virginia  Amniocentesis in twin gestations	
Charleston  Gainesville  The effect with the and Amnon M Haifa, Isra  Obst  Plasma V Narinder M Charleston Genetic and Sherman H	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D. at least of the column expansion in the treatment of pre-eclampsia J. Sehgal, M.D., and John R. Hitt, M.D. at least virginia	165
Charleston  Gainesville  The effect with the and the second of the secon	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.  The second of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.  The second of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.  The second of the multiple-exposure photography method akler, M.D., and John R. Hitt, M.D.  The second of the multiple-exposure photography method akler, M.D., and John R. Hitt, M.D.  The second of the multiple-exposure photography method akler, M.D., and John R. Hitt, M.D.  The second of the multiple-exposure photography method akler, M.D., and John R. Hitt, M.D.  The second of the multiple-exposure photography method akler, M.D., and John R. Hitt, M.D.  The second of the multiple-exposure photography method akler, M.D., and John R. Hitt, M.D.  The second of the multiple-exposure photography method akler, M.D., and John R. Hitt, M.D.  The second of the multiple-exposure photography method akler, M.D., and John R. Hitt, M.D.  The second of the multiple-exposure photography method akler, M.D., and John R. Hitt, M.D.  The second of the multiple-exposure photography method akler, M.D., and John R. Hitt, M.D.  The second of the multiple-exposure photography method akler, M.D., and John R. Hitt, M.D.  The second of the multiple-exposure photography method akler, M.D., and John R. Hitt, M.D.  The second of the multiple-exposure photography method akler, M.D., and John R. Hitt, M.D.  The second of the multiple-exposure photography method akler, M.D., and John R. Hitt, M.D.  The second of the multiple-exposure photography method akler, M.D., and Arnold Shkolnik, M.D.	165
Chicago, A	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.  Petrics  Colume expansion in the treatment of pre-eclampsia  N. Sehgal, M.D., and John R. Hitt, M.D.  N. West Virginia  Commiscentesis in twin gestations  Clias, M.D., Albert B. Gerbie, M.D., Joe Leigh Simpson, M.D.,  Nadler, M.D., Rudy E. Sabbagha, M.D., and Arnold Shkolnik, M.D.  Collinois	169
Chicago, A simplifi	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.  Petrics  Colume expansion in the treatment of pre-eclampsia  N. Sehgal, M.D., and John R. Hitt, M.D.  N. West Virginia  Commiscentesis in twin gestations  Clias, M.D., Albert B. Gerbie, M.D., Joe Leigh Simpson, M.D.,  Nadler, M.D., Rudy E. Sabbagha, M.D., and Arnold Shkolnik, M.D.  Millinois  iled intrapartum numerical scoring system	169
Chicago, A simplif	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.  Petrics  Colume expansion in the treatment of pre-eclampsia  N. Sehgal, M.D., and John R. Hitt, M.D.  N. West Virginia  Commiscentesis in twin gestations  Clias, M.D., Albert B. Gerbie, M.D., Joe Leigh Simpson, M.D.,  Nadler, M.D., Rudy E. Sabbagha, M.D., and Arnold Shkolnik, M.D.  Collinois	165
Charleston  Genetic a Sherman H Henry L. Chicago, A  A simplifi Ian Morris and Mary	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D. at the local section of the expansion in the treatment of pre-eclampsia of the expansion in the treatment of pre-eclampsia of the expansion in the treatment of pre-eclampsia of the expansion of the expansion of the expansion in the treatment of pre-eclampsia of the expansion of the expansio	165
Charleston  Genetic a Sherman I Henry L. Chicago, A  A simplif Ian Morris and Mary Winnipeg,	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.  Petrics  Colume expansion in the treatment of pre-eclampsia  N. Sehgal, M.D., and John R. Hitt, M.D.  N. West Virginia  Amniocentesis in twin gestations  Clias, M.D., Albert B. Gerbie, M.D., Joe Leigh Simpson, M.D.,  Nadler, M.D., Rudy E. Sabbagha, M.D., and Arnold Shkolnik, M.D.  Illinois  ied intrapartum numerical scoring system  on, M.B., Ch.B., F.R.C.S.(C.), Lorraine Carter, R.N., Sharilyn McNamara, R.N.,  Cheang, M.Math.  Manitoba, Canada	165 165
Plasma V Narinder N Charleston Genetic a Sherman H Henry L. Chicago, A A simplif Ian Morris and Mary Winnipeg, Electroca	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.  Petrics  Colume expansion in the treatment of pre-eclampsia  N. Sehgal, M.D., and John R. Hitt, M.D.  N. West Virginia  Commission in twin gestations  Clias, M.D., Albert B. Gerbie, M.D., Joe Leigh Simpson, M.D.,  Nadler, M.D., Rudy E. Sabbagha, M.D., and Arnold Shkolnik, M.D.  Illinois  Ited intrapartum numerical scoring system  On, M.B., Ch.B., F.R.C.S.(C.), Lorraine Carter, R.N., Sharilyn McNamara, R.N.,  Cheang, M.Math.  Manitoba, Canada  Cardiographic changes induced by suction curettage for elective	165
Plasma Warinder Marinder Marin	t of copper on spermatozoal motility and viability evaluated objectively aid of the multiple-exposure photography method akler, M.D., and Oren Zinder, Ph.D.  Petrics  Colume expansion in the treatment of pre-eclampsia  N. Sehgal, M.D., and John R. Hitt, M.D.  N. West Virginia  Amniocentesis in twin gestations  Clias, M.D., Albert B. Gerbie, M.D., Joe Leigh Simpson, M.D.,  Nadler, M.D., Rudy E. Sabbagha, M.D., and Arnold Shkolnik, M.D.  Illinois  ied intrapartum numerical scoring system  on, M.B., Ch.B., F.R.C.S.(C.), Lorraine Carter, R.N., Sharilyn McNamara, R.N.,  Cheang, M.Math.  Manitoba, Canada	165 165



#### present

#### The TENTH ANNUAL REVIEW COURSE IN GYNECOLOGY AND OBSTETRICS

This comprehensive course will be held at the Pasadena Hilton Hotel, Pasadena, California, Monday through Friday, January 26-30, 1981. It will review many basic concepts and update clinical management in every area of obstetrics and gynecology. Although the program will appeal to all, its direction will be toward those preparing for recertification examinations or the Oral OB/GYN Boards. A complete, well-organized syllabus covering the entire five-day program will be supplied each participant.

TUITION: \$400 (includes 5 lunches)

CREDIT: 36 hours

Immediately following is the REVIEW COURSE FOR GYNECOLOGIC PATHOLOGY, scheduled for Saturday, January 31, 1981, at the USC School of Medicine Health Sciences Campus. Review of pathological changes which occur in the female genital tract in response to inflammatory, neoplastic and abnormal hormonal stimuli as well as concepts of diagnosis and pathogenesis will be discussed; current terminology used in diagnosis will be emphasized. This course is designed primarily to assist those physicians who are preparing for the American Board of Obstetrics and Gynecology examinations.

TUITION: \$55.00 (includes lunch)

CREDIT: 6 hours

Contact: Associate Dean

USC School of Medicine Postgraduate Division 2025 Zonal Avenue Los Angeles, CA 90033

Phone: (213) 224-7051

### CLINICAL BIOSTATISTICS:

# here's why you'll benefit from this book

- authoritative articles from <u>Clinical Pharmacology and</u> Therapeutics
- clear and easy-to-read explanations of essential statistical concepts
- provocative insights into the common sense and science behind statistical data

#### CLINICAL BIOSTATISTICS

This unique book critically examines the entire field of clinical biostatistics. It presents a series of original articles that first appeared over a five year period in *Clinical Pharmacology and Therapeutics*. Widespread reader acclaim and the timeliness of the subject prompted publication of the essays into convenient book form.

The essays are logically arranged into 29 chapters and organized into five major sections, each preceded by brief commentary written especially for the book. You'll find informative discussions on the diverse statistical techniques used in medical practice and research; research and design problems; presentation of data; and methods of data analysis. Dr. Feinstein has reorganized his original articles to provide you with a completely current guide to the biostatistics used in both clinical and investigative situations. He also offers valuable insights into topics either totally neglected or inadequately covered in conventional texts. Throughout, discussions are written in lively prose style, which makes the subject both interesting to read and easy-to-understand. Why not benefit from Dr. Feinstein's expert guidance firsthand-order your copy of CLINICAL BIOSTATISTICS today!

By Alvan R. Feinstein, M.D., 1977, 468 pages plus FM I-XIV, 6-7/8" x 10", 10 illustrations. Price, \$21.50

#### **ORDER BY PHONE!**

Call toll free (800) 325-4177 ext. 10. In Missouri Call collect—(314) 872-8370 ext. 10 during normal business hours.

A80794
Price effective in U.S.A. only.

MOSBY TIMES MIRROR

THE C V MOSBY COMPANY 11830 WESTLINE INDUSTRIAL DRIVE ST LOUIS MISSOURI 63141

#### Contents continued from page 7

ed cell exchange in the pregnancy complicated by a major hemoglobinopathy	185
Iarie M. Keeling, M.D., J. Patrick Lavery, M.D., Anita U. Clemons, Robert L. Schaefer,	
atricia D. Blandford, and Estus A. Harris	
ouisville, Kentucky	
	189
soelectric heterogeneity of human chorionic gonadotropin: Presence of	109
horiocarcinoma specific components	
Katsumi Yazaki, M.D., Chiaki Yazaki, M.D., Katsumi Wakabayashi, Ph.D., and	
Masao Igarashi, M.D.	
Aaebashi, Japan	
Fetus, placenta, and newborn	
Nonstress testing	195
Allan B. Weingold, M.D., M. Lynn Yonekura, M.D., and Jane O'Kieffe, B.A.	
Washington, D. C.	
	203
Intravenous dexamethasone for prevention of neonatal respiratory distress:	203
A prospective controlled study	
Bruce K. Young, M.D., F.A.C.O.G., Steven A. Klein, M.D., F.A.C.O.G.,	
Miriam Katz, M.D., Stephen J. Wilson, M.D., and Gordon W. Douglas, M.D., F.A.C.O.G.	
New York, New York	
Clinical significance of perceptible fetal motion	210
William F. Rayburn, M.D.	
Columbus, Ohio	
	213
Intrapartum fetal heart rate monitoring. IV. Observations on elective and	210
nonelective fetal heart rate monitoring	
H. B. Krebs, M.D., R. E. Petres, M.D., L. J. Dunn, M.D., and A. Segreti, Ph.D.	
Richmond, Virginia	
Re-evaluation of birth weights at high altitude	220
Ernest K. Cotton, M.D., Mahlon Hiestand, M.D., George E. Philbin, M.D., and	
Michael Simmons, M.D.	

#### An alternative to antepartum fetal heart rate testing

223

William Rayburn, M.D., Frederick Zuspan, M.D., Mary Ellen Motley, L.P.N., and Marcia Donaldson, R.N.

Lexington, Kentucky, and Columbus, Ohio

(Contents continued on page 11)

# Just tell us where you want to live.

Hospital Corporation of America assists hundreds of physicians in locating solid practice opportunities each year. With HCA, you can choose a community that fits your lifestyle and know that the local hospital's staff and facilities will reflect your own high professional standards.

HCA owns or manages over 150 hospitals from San Francisco to Virginia...from Boston to Miami. Each hospital is well equipped, and professionally accredited and staffed. Practice opportunities are available in solo, groups, associations and available in solo, groups, associations are available in solo, groups, associations and available in solo, groups, associations are available in solo, groups, associations and available in solo, groups, associations are available in solo, as a solo and a solo available are available are available and a solo available are a

ciations and partnerships.

Contact HCA today. Let our free, no obligation Professional Relations Program match your needs with an HCA practice opportunity. Just send your <u>curriculum vitae</u>, with information on your personal, professional, and geographic interests, to: Charles M. Wooden, Director, Professional Relations, Hospital Corporation of America, One Park Plaza, Nashville, TN 37203. Telephone toll free 1-800-251-2561 or call collect (615) 327-9551.



Hospital Corporation of America.

## TEACHING HOSPITAL KING FAISAL UNIVERSITY COLLEGE OF MEDICINE SAUDI ARABIA

The new 380-bed AlKhobar Teaching Hospital, affiliated with King Faisal University College of Medicine, Eastern Province, Saudi Arabia, invites applications from board certified clinicians in:

#### **OBSTETRICS AND GYNECOLOGY**

SALARIES highly competitive and negotiable. Instruction is in English. Interviews scheduled during late-1980 and early-1981. CONTRACTS are for one year and renewable. Clinicians hold faculty appointments.

BENEFITS include free furnished housing, airtickets to and from Saudi Arabia one time each year for a family of four, 60-day vacation with pay, generous overweight and educational allowances. No Saudi income tax.

Please send curriculum vitae with current telephone numbers, and the names and addresses of three references to:

Dr. Tawfiq Tamimi, Dean College of Medicine, King Faisal University

c/o Saudi Arabian Educational Mission 2425 West Loop South Houston, TX 77027 P.O. Box 2 Sunbury-on-Thames Middlesex TW16 5JP England

## OBSTETRICIAN/ GYNECOLOGIST

Board certified/eligible Ob-Gyn wanted for group in lovely S.E. Mass. community.
One office-one hospital.
Unique coverage schedule with a second group currently allows every eighth night call.
No pregnancy terminations.
Great opportunity.

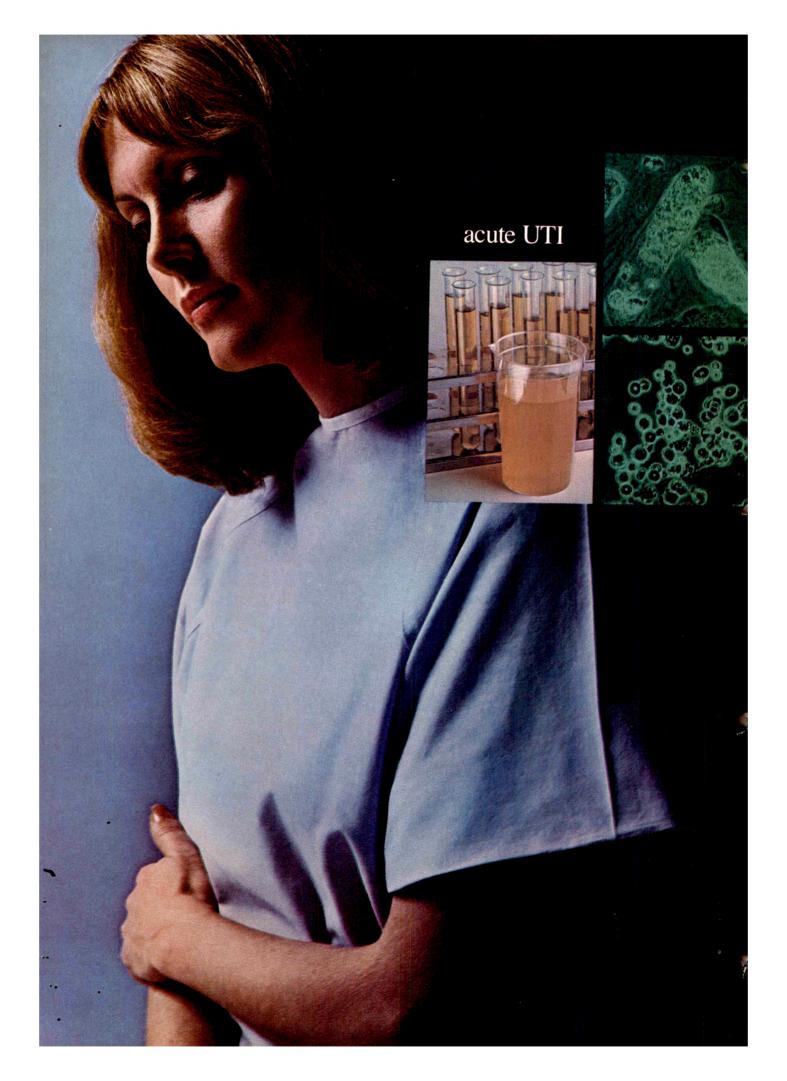
Contact:
T. P. McCORMACK, M.D.
60 Brigham St.
New Bedford, Ma., 02740.
Phone: 617-997-2200

#### Communications in brief

Significance of fetal and neonatal sinusoidal heart rate pattern: Further clinical observations in Rh incompatibility	227
John P. Elliott, M.D., Major, MC, USA, Houchang D. Modanlou, M.D.,	
Daniel F. O'Keeffe, M.D., and Roger K. Freeman, M.D.	
Long Beach and Orange, California	
Pseudocyesis and sonography	230
Gay M. Guzinski, M.D., and Suzanne H. Conrad, M.D.	
Seattle, Washington	
Lecithin/sphingomyelin ratio in amniotic fluid obtained vaginally	232
Arnold S. Goldstein, M.D., Henry H. Mangurten, M.D., Joseph V. Libretti, M.D.,	
and Arnold M. Berman, M.D.	
Park Ridge, Illinois	
Accidental puncture of pelvic kidney: A rare complication of culdocentesis	233
Menachem Granat, M.D., Thomas Gordon, M.D., Elias Issaq, M.D., and	
Moshe Shabtai, M.D.	
Haifa, Israel	
Real-time ultrasonography in the evaluation of urinary stress incontinence	235
Rolfe D. White, M.D., Lieutenant, MC, USNR, Dennis McQuown, M.D.,	
Thomas A. McCarthy, M.D., and Donald R. Ostergard, M.D., F.A.C.O.G.	
Long Beach and Torrance, California, and Portsmouth, Virginia	
Oral contraceptive-induced chorea	237
Naomi Kaplinsky, M.D., Michael Thaler, M.D., and Otto Frankl, M.D.	
Tel-Hashomer, Israel	
Books	
Books received	238
	5
Erratum	
Correction of article by Das and Foster, entitled "Amniotic fluid lipids in sickle	226
cell disease"	

Information for authors on page 23

Index to advertisers on page 48



#### In acute UTI

# When your first choice is Macrodantin you'll rarely need a second one

Macrodantin is potent against both major uropathogens in office practice—*E. coli*, the most common, and *enterococcus*—unlike other widely prescribed antimicrobials used individually or in combination.

Superior in vitro\* against the two most common uropathogens

E. coli			Enterococcus	a mideral life	
MACRODANTIN		97%	MACRODA	NTIN	94%
TMP/SMX		95%	TMP/SMX	51%	
Sulfonamide	73%		Sulfonami	ide 6%	

<sup>\*</sup>In vitro data do not necessarily predict clinical efficacy.

#### Macrodantin remains consistently effective year after year—resistance is negligible

- Does not foster resistant bowel flora which may recycle infection.
- Does not change normal vaginal flora...little risk of Candida overgrowth.
- Concentrates its action in the urinary tract.

Lets you reserve systemic agents for systemic infection.

...too valuable to keep in reserve

# Macrodantin Capsules: 25,50,100mg (nitrofurantoin macrocrystals)

Norwich-Eaton

Norwich, New York 13815
Division of MortonNorwich Products, Inc.

<sup>1.</sup> PMR Bacteriologic Report, Summer Series 1979;

a national bacteriologic monitoring service for 200 acute-care hospitals of 100 beds or more.

#### ...too valuable to keep in reserve

#### **Macrodantin**<sup>®</sup>

#### (nitrofurantoin macrocrystals)

Capsules: 25,50,100mg

INDICATIONS: Macrodantin is indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus* (it is not indicated for the treatment of associated renal cortical or perinephric abscesses), and certain susceptible strains of *Klebsiella* species, *Enterobacter* species, and *Proteus* species.

NOTE: Specimens for culture and susceptibility testing should be obtained prior to and during drug administration.

CONTRAINDICATIONS: Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 40 ml per minute) are contraindications to therapy with this drug. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of the drug. For the same reason, this drug is much less effective under these circumstances.

The drug is contraindicated in pregnant patients at term as well as in infants under one month of age because of the possibility of hemolytic anemia due to immature enzyme systems (glutathione instability).

The drug is also contraindicated in those patients with known hypersensitivity to Macrodantin, Furadantin® (nitrofurantoin), and other nitrofurantoin preparations.

WARNINGS: Acute, subacute and chronic pulmonary reactions have been observed in patients treated with nitrofurantoin products. If these reactions occur, the drug should be withdrawn and appropriate measures should be taken.

An insidious onset of pulmonary reactions (diffuse interstitial pneumonitis or pulmonary fibrosis, or both) in patients on long-term therapy warrants close monitoring of these patients.

There have been isolated reports giving pulmonary reactions as a contributing cause of death. (See Hypersensitivity reactions.)

Cases of hemolytic anemia of the primaquine sensitivity type have been induced by Macrodantin. The hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Negroes and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Any sign of hemolysis is an indication to discontinue the drug. Hemolysis ceases when the drug is withdrawn.

Pseudomonas is the organism most commonly implicated in superinfections in patients treated with Macrodantin.

Hepatitis, including chronic active hepatitis, has been observed rarely. Fatalities have been reported. The mechanism appears to be of an idiosyncratic hypersensitive type.

PRECAUTIONS: Peripheral neuropathy may occur with Macrodantin therapy; this may become severe or irreversible. Fatalities have been reported. Predisposing conditions such as renal impairment (creatinine clearance under 40 ml per minute), anemia, diabetes, electrolyte imbalance, vitamin B deficiency, and debilitating disease may enhance such occurrence.

Usage in Pregnancy: The safety of Macrodantin during pregnancy and lactation has not been established. Use of this drug in women of childbearing potential requires that the anticipated benefit be weighed against the possible risks.

ADVERSE REACTIONS: Gastrointestinal reactions: Anorexia, nausea and emesis are the most frequent reactions; abdominal pain and diarrhea occur less frequently. These dose-related toxicity reactions can be minimized by reduction of dosage, especially in the female patient. Hepatitis occurs rarely.

**Hypersensitivity reactions:** Pulmonary sensitivity reactions may occur, which can be acute, subacute, or chronic.

Acute reactions are commonly manifested by fever, chills, cough, chest pain, dyspnea, pulmonary infiltration with consolidation or pleural effusion on x-ray, and eosinophilia. The acute reactions usually occur within the first week of treatment and are reversible with cessation of therapy. Resolution may be dramatic.

In subacute reactions, fever and eosinophilia are observed less often. Recovery is somewhat slower, perhaps as long as several months. If the symptoms are not recognized as being drug related and nitrofurantoin is not withdrawn, symptoms may become more severe.

Chronic pulmonary reactions are more likely to occur in patients who have been on continuous nitrofurantoin therapy for six months or longer. The insidious onset of malaise, dyspnea on exertion, cough, and altered pulmonary function are common manifestations. Roentgenographic and histologic findings of diffuse interstitial pneumonitis or fibrosis, or both, are also common manifestations. Fever is rarely prominent.

The severity of these chronic pulmonary reactions and the degree of their resolution appear to be related to the duration of therapy after the first clinical signs appear. Pulmonary function may be permanently impaired even after cessation of nitrofurantoin therapy. This risk is greater when pulmonary reactions are not recognized early.

Dermatologic reactions: Maculopapular, erythematous, or eczematous eruption, pruritus, urticaria, and angioedema.

Other hypersensitivity reactions: Anaphylaxis, asthmatic attack in patients with history of asthma, cholestatic jaundice, hepatitis, including chronic active hepatitis, drug fever, and arthrelaid.

Hematologic reactions: Hemolytic anemia, granulocytopenia, leukopenia, eosinophilia, and megaloblastic anemia. Return of the blood picture to normal has followed cessation of therapy.

Neurological reactions: Peripheral neuropathy, headache, dizziness, nystagmus, and drowsiness.

Miscellaneous reactions: Transient alopecia. As with other antimicrobial agents, superinfections
by resistant organisms may occur. With Macrodantin, however, these are limited to the genitourinary tract because suppression of normal bacterial flora elsewhere in the body does not
ocour.

#### Eaton Laboratories Inc.

A subsidiary of MortonNorwich Products, Inc., Manati, Puerto Rico 00701

\*\*Address medical inquiries to: Norwich-Eaton Pharmaceuticals, Medical Department, Norwich, New York 13815

#### EDITORS! REVIEWERS! AUTHORS!

For you . . . a new book that contains virtually everything you want to know about

#### THE SCIENTIFIC JOURNAL: EDITORIAL POLICIES AND PRACTICES

#### Guidelines for Editors, Reviewers, and Authors

In 1665 the first scholarly journal was published in France. Since that time, there has been no one source of editorial guidelines for journal editors. This new book now provides you with such a source.

#### YOU DECIDE YOUR OWN APPROACH!

Presenting the advantages and disadvantages of each specific decision, eminent editors offer you various recommendations, discussions, and opinions concerning the problems you may encounter:

"Because we are aware that there is no 'right' policy on most editorial matters, we have tried not to prescribe rules, but have, instead, explored various facets of the problems that confront the editor in his daily work."

The book is divided into two general sections: editorial policies, which usually require major decisions; and editorial practices, which involve minor decisions, often about format or mechanical style. You'll find essays exploring: the manuscript reviewing system; special types of manuscripts (abstracts, transactions, solicited manuscripts, book reviews). You'll value chapters which cover: information for authors; copyright; errata; references cited; copy-editing; journal cover; etc.

From "the purpose of scientific journals" to "binding practices," this new book contains virtually everything you want to know as editor, reviewer, or author. See for yourself!

By Lois DeBakey, Ph.D. In collaboration with: Paul F. Cranefield, M.D., Ph.D.; Ayodhya P. Gupta, M.D.; Franz J. Ingelfinger, M.D.; Robert J. Levine, M.D.; Robert H. Moser, M.D.; J. Roger Porter, Ph.D.; and F. Peter Woodford, Ph.D. August, 1976. 128 pages, 6" × 9". Price, \$12.50.

Please send JOURNAL:	me on 30-day approx EDITORIAL POLICIES	val THE SCIENTIFIC
Price, \$12.50.		•
□ Bill me	☐ Master Charge #_	
☐ Payment e	enclosed	
Name		
Address		
City		
State	Zip	Code
	r	MOSBY

30-day approval offer good only in continental U.S. and Canada.

TIMES MIRROR

THE C. V. MOSBY COMPANY

11830 WESTLINE INDUSTRIAL DRIVE

ST. LOUIS, MISSOURI 63141

#### American Journal of Obstetrics and Gynecology

#### **Editors**

JOHN I. BREWER, Editor in Chief

FREDERICK P. ZUSPAN, E. J. QUILLIGAN, Editors

ALBERT B. GERBIE, Associate Editor

HOWARD C. TAYLOR, JR., ALLAN C. BARNES, Emeritus Editors

#### Advisory committee on policy

C. D. Christian

Leo J. Dunn

George D. Malkasian

David Figge

Roy T. Parker

W. Ann Reynolds

A. Brian Little

J. C. G. Whetham

#### **Board** of corresponding editors

Oscar Aguero, Caracas
Frederick Kubli, Heidelberg
Pierre O. Hubinont, Brussels
Malcolm Symonds, Nottingham
Ichiro Taki, Fukuoka

# HER OCISIT FOR BETTER OR WORSE.

If it's NORLESTRIN® 1/50 (I mg norethindrone acetate and 50 mcg ethinyl estradiol tablets, USP), it's exactly what she expects...and it's exactly what you've come to expect in terms of efficacy and patient acceptance. Ever since NORLESTRIN 1/50 was first introduced over a decade ago, it has performed as promised, consistently providing what patients and their physicians want from an OC: virtually complete control of conception plus relative freedom from annoying side effects like breakthrough bleeding.

With its combination of ethinyl estradiol and norethindrone acetate, NORLESTRIN 1/50 gives patients the comfort and confidence they look for in an OC. Cycle after cycle, NORLESTRIN 1/50 gives your patient no more estrogen than she needs.

## NORLESTRIN

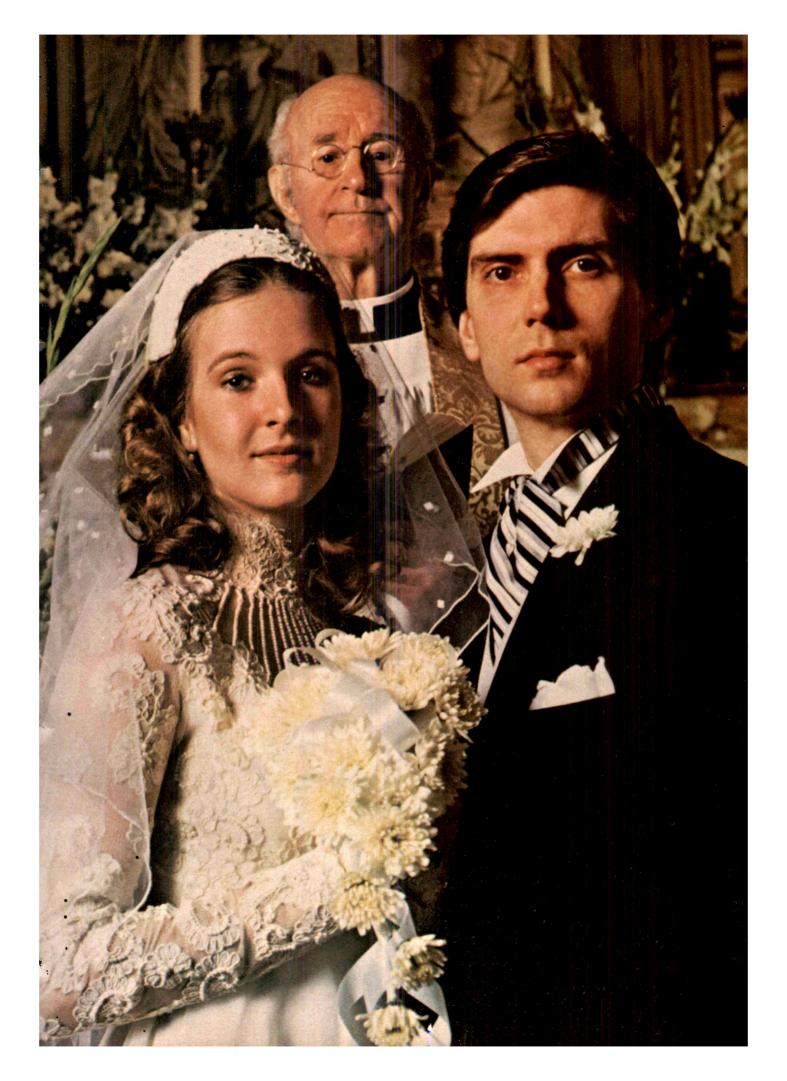
(1 mg norethindrone acetate and 50 mcg ethinyl estradiol tablets, USP)

YOU COULDN'T DO BETTER.

Please see following page for brief summary of prescribing information.

PARKE-DAVIS

© 1980 Warner-Lambert Company



#### Brief Summary of Prescribing Information. NORLESTRIN® 1/50

(norethindrone acetate and ethinyl estradiol tablets, USP) See section under Special Notes on Administration and HOW SUPPLIED.

Each yellow tablet contains: norethindrone acetate (17 alpha-ethinyl-19-nortestosterone acetate), 1 mg; ethinyl estradiol (17 alpha-ethinyl-1,3,5(10)-estratriene-3, 17 beta-diol), 50

Norlestrin 1/50 Products are progestogen-estrogen combinations.

INDICATIONS AND USAGE

Norlestrin 1/50 Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception

In clinical trials with Norlestrin 1/50 involving 25,983 therapy cycles, there was a preg-

nancy rate of 0.05 per 100 women years.

Dose-related risk of thromboembolism from oral contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance.

CONTRAINDICATIONS

- Thrombophlebitis or thromboembolic disorders
  A past history of deep-vein thrombophlebitis or thromboembolic disorders

A past instory of deep-vent information to inform the Cerebral vascular or coronary artery disease Known or suspected carcinoma of the breast Known or suspected estrogen-dependent neoplasia Undiagnosed abnormal genital bleeding Known or suspected pregnancy (See WARNING No. 5.)

#### WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to

or age. World's with use some sample.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these

1. Thromboembolic Disorders and Other Vascular Problems: An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-

boembolic and thrombotic disease associated with the use of oral contraceptives is wellestablished. Studies have demonstrated an increased risk of fatal and nonfatal venous
thromboembolism and stroke, both hemorrhagic and thrombotic.

Cerebrovascular disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in
users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater.

Myocardial infarction: An increased risk of myocardial infarction associated with oral
contraceptives has been reported confirming a previously suspected association. These
studies found that the greater the number of underlying risk factors (cigarette smoking,
hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for
coronary artery disease, the higher the risk of developing myocardial infarction, regardless
of whether the patient was an oral contraceptive user or not. Oral contraceptives, however,
were found to be a clear additional risk factor. were found to be a clear additional risk factor.

were found to be a clear additional risk factor. It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke. The amount of smoking is also an important factor.

Risk of dose: In an analysis of data. British investigators confuded that the risk of thrombonembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives; however, the quantity of estrogen may not be the sole factor involved.

Estimate of excess mortality from circulatory diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in

latory system is concentrated in older women, in those with a long duration of use, and in

Latinate of excess mortainty from circulatory diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers.

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke.

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increased with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preclamptic toxemia, and especially by cigarette smoking.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders. Should any occur or be suspected, the drug should be discontinued immediately.

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

2. Ocular lesions: Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision; cnset of proptosis or diplopia; papilledema; or retinal vascular lesions.

3. Carcinoma: Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver.

3. Carcinoma: Long-term continuous administration or estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver. In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported. However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives.
Studies found no evidence of increase in breast cancer in women taking oral contraceptives; however, an excess risk in users with documented benign breast disease was reported.

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of users is, nevertheless, essential. In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of bleast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms, which we may be the strong that the production of the contraction of the con

Dast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care.

4. Hepatic Tumors: Benign hepatic adenomas have been found to be associated with oral contraceptives. Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. Usage in or Immediately Preceding Pregnancy; Birth Defects in Offspring, and Malignancy in Female Offspring: During early pregnancy, female sex hormones may seriously damage the offspring.

nancy in Female Utspring: During early pregnancy, female sex normones may seriously damage the offspring.

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy.

There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptions.

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods. If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed.

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive. Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. Gallbiadder Disease: Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives.

6. Gallbladder Disease: Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives.
7. Carbohydrate and Lipid Metabolic Effects: Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.
An increase in triglycerides and total phospholipids has been observed.
8. Elevated Blood Pressure: An increase in blood pressure has been reported in patients receiving oral contraceptives. The prevalence in users increases with longer exposure. Age is also strongly correlated with development of hypertension. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure.

9. Headache: Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contracep-

tives.

10. Bleeding Irregularities: Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, nonfunctional causes should be borne in mind. In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives.

11. Ectopic Pregnancy: Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

ve failures

12. Breast Feeding: Oral contraceptives may interfere with lactation. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of ing these drugs

#### PRECAUTIONS

PRECAUTIONS

1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.

2. Preexisting uterine leiomyomata may increase in size.

3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

4. Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice. If jaundice develops, the medication should be discontinued.

6. Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function.

7. Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency.

8. Serum folate levels may be depressed.

9. The pathologist should be advised of oral contraceptive therapy when relevant specimes are submitted.

mens are submitted.

mens are submitted.

10. Certain endocrine and liver function tests and blood components may be affected.

(a) Increased sulfobromophthalein retention. (b) Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone. (d) Decreased pregnanediol excretion. (e) Reduced response to metyrapone test.

Drug interactions: Reduced efficacy and increased incidence of breakthrough bleeding ave been associated with concomitant use of rifampin and an association has been uggested with barbiturates, phenylbutazone, phenytoin sodium, and ampicillin.

#### ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with oral contraceptives: thrombophlebitis; pulmonary embolism; coronary thrombosis cerebral thrombosis; cerebral hemorrhage; hypertension; gallbladder disease; benign hepatomas; congenital anomalies.

There is evidence of an association between the following conditions and the use of oral

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, eg., refinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related: nausea and/or vomiting, usually the most comen adverse reactions, occur in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally; gastrointestinal symptoms; breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma; breast changes, change in weight; change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately post partum; cholestatic jaundice; migraine; increase in size of uterine eiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature; intolerance to contact lenses.

The following adverse reactions have been reported and the association has been neither confirmed nor refuted; premenstrual-like syndrome; cataracts; changes in libido; chorea; changes in appetite; cystitis-like syndrome; erythema nodosum; hemorrhagic eruption; vaginitis; porphyria.

porphyria.

Special Notes on Administration

Ncriestrin [Fe] 1/50 (norethindrone acetate and ethinyl estradiol tablets, USP) and Norlestrin [Z8] 1/50—Menstruation usually begins two or three days, but may begin as late as the fourth or lifth day, after the brown ferrous fumarate or white inert tablets have been started. Norlestrin [Z1] 1/50—Menstruation usually begins two or three days, but may begin as late as the fourth or lifth day, after discontinuing medication.

After several months on treatment, bleeding may be reduced to a point of virtual absence; reduced flow may be a result of medication and not indicative of pregnancy.

HOW SUPPLIED

Nortestrin [Fe] 1/50 is available in migrographs each containing (1 vallow tablets and 7).

HOW SUPPLIED

Nortestrin [E] 1/50 is available in minicompacts each containing 21 yellow tablets and 7 brown tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate. Available in packages of five minicompacts and packages of five refills.

Nortestrin [28] 1/50 is available in minicompacts each containing 21 yellow tablets and 7 white inert tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five minicompacts and in packages of five refils.

Nortestrin [27] 1/50 is available in minicompacts each containing 21 yellow tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five minicompacts and packages of five refills.

YB

PARKE-DAVIS

Div of Warner-Lambert Co Morris Plains, NJ 07950 USA

#### American Journal of Obstetrics and Gynecology

in addition to those listed on the front cover the Journal is the official publication of the following societies

NEW YORK OBSTETRICAL SOCIETY OBSTETRICAL SOCIETY OF PHILADELPHIA BROOKLYN GYNECOLOGICAL SOCIETY ST. LOUIS GYNECOLOGICAL SOCIETY NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY THE OBSTETRICAL AND GYNECOLOGICAL SOCIETY OF MARYLAND CHICAGO GYNECOLOGICAL SOCIETY CINCINNATI OBSTETRICAL AND GYNECOLOGICAL SOCIETY WASHINGTON GYNECOLOGICAL SOCIETY PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY BOSTON OBSTETRICAL SOCIETY LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY SEATTLE GYNECOLOGICAL SOCIETY ALABAMA ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS AKRON OBSTETRICAL AND GYNECOLOGICAL SOCIETY KANSAS CITY GYNECOLOGICAL SOCIETY CENTRAL NEW YORK ASSOCIATION OF GYNECOLOGISTS

AND OBSTETRICIANS

NEW JERSEY OBSTETRICAL AND GYNECOLOGICAL SOCIETY IOWA OBSTETRIC AND GYNECOLOGIC SOCIETY THE TEXAS ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS OKLAHOMA CITY OBSTETRICAL AND GYNECOLOGICAL SOCIETY MEMPHIS OBSTETRICAL AND GYNECOLOGICAL SOCIETY UTAH OBSTETRICAL AND GYNECOLOGICAL SOCIETY ROCHESTER OBSTETRICAL AND GYNECOLOGICAL SOCIETY ARKANSAS OBSTETRICAL AND GYNECOLOGICAL SOCIETY TENNESSEE STATE OBSTETRICAL AND GYNECOLOGICAL SOCIETY NEW YORK GYNECOLOGICAL SOCIETY PACIFIC NORTHWEST OBSTETRICAL AND GYNECOLOGICAL ASSOCIATION BUFFALO OBSTETRICAL AND GYNECOLOGICAL SOCIETY SAN FRANCISCO GYNECOLOGICAL SOCIETY JACKSON GYNECIC SOCIETY INDIANA OBSTETRICAL AND GYNECOLOGICAL SOCIETY THE MINNESOTA OBSTETRICAL AND GYNECOLOGICAL SOCIETY

Proven highly effective for the treatment of serious infections\*

# Mefoxin "IM" (Cefoxitin Sodium | MSD)

VIALS, containing 1 gram and 2 grams cefoxitin equivalent

\*Due to susceptible strains of indicated bacteria at indicated sites.

Copyright © 1980 by Merck & Co., Inc. All rights reserved.

# Now Indicated for prophylaxis to reduce the incidence of certain postoperative infections complicating

GI surgery • Vaginal hysterectomy • Cesarean section •

Providing a broad spectrum—including Bacteroides fragilis

In controlled clinical trials, MEFOXIN® (Cefoxitin Sodium, MSD) reduced the incidence of certain postoperative infections

with use limited to a 24-hour period following the operative procedure.

Prophylactic administration should usually be stopped within 24 hours since continuing administration of any antibiotic increases the possibility of adverse reactions.

†Perioperatively: Two grams administered intravenously or intramuscularly just prior to surgery (approximately ½ to 1 hour before the initial incision); then 2 grams every 6 hours for no more than 24 hours.

‡Cesarean-section patients: The first dose of 2 grams is administered intravenously as soon as the umbilical cord is clamped. The second and third doses should be given as 2 grams intravenously or intramuscularly 4 hours and 8 hours after the first dose. Subsequent doses may be given every 6 hours for no more than 24 hours.

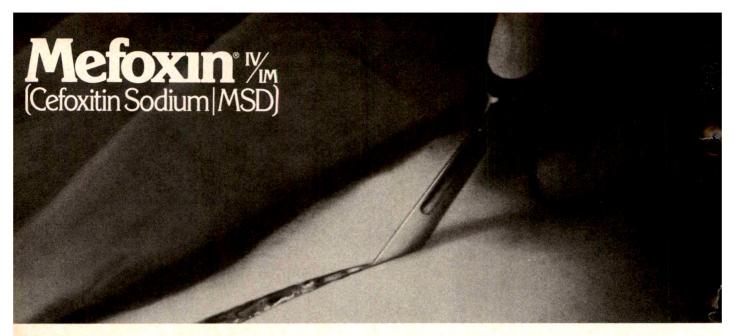
For complete details on dosage and administration, see full prescribing information.

If there are signs of infection, specimens for

of the causative organisms so that appropriate therapy may be instituted.

MEFOXIN (Cefoxitin Sodium, MSD) is contraindicated in patients who have shown hypersensitivity to cefoxitin and the cephalosporin group of antibiotics. Before therapy with MEFOXIN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefoxitin, cephalosporins, penicillins, or other drugs. This product should be given with caution to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to MEFOXIN occurs, discontinue the drug. Serious hypersensitivity reactions may require epinephrine and other emergency measures. Use of the drug in women of childbearing potential requires that the anticipated benefit be weighed against the possible risks.

For a brief summary of prescribing in formation



Indications and Usage: Treatment - Serious infections caused by susceptible strains of the designated microorganisms in the following

LOWER RESPIRATORY TRACT INFECTIONS, including pneumonia and lung abscess, caused by Streptococcus pneumoniae (formerly Diplococcus pneumoniae), other streptococci (excluding enterococci, an Streptococci). e.g., Strep. faecalis), Staphylococcus aureus (penicillinase and non-penicillinase producing), Escherichia coli, Klebsiella species, Hemophilus influenzae, and Bacteroides species.

GENITOURINARY INFECTIONS. Urinary tract infections caused by E. coli, Klebsiella species, Proteus mirabilis, indole-positive Proteus

(i.e., P. morganii, P. rettgeri, and P. vulgaris), and Providencia species. Uncomplicated gonorrhea due to Neisseria gonorrhoeae.

INTRA-ABDOMINAL INFECTIONS, including peritonitis and intraabdominal abscess, caused by E. coli, Klebsiella species, Bacteroides species including the *B. fragilis* group,‡ and *Clostridium* species.

GYNECOLOGICAL INFECTIONS, including endometritis, pelvic cellulitis, and pelvic inflammatory disease, caused by E. coli, N. gonor-rhoeae, Bacteroides species including the B. fragilis group,‡ Clostridium species, Peptococcus species, Peptostreptococcus species, and group B streptococci.

and group B streptococci.

SEPTICEMIA caused by Strep. pneumoniae (formerly D. pneumoniae), Staph. aureus (penicillinase and non-penicillinase producing), E. coli, Klebsiella species, and Bacteroides species including the B. fragilis group.‡

BONE AND JOINT INFECTIONS caused by Staph. aureus (penicil-

linase and non-penicillinase producing).
SKIN AND SKIN STRUCTURE INFECTIONS caused by Staph. aureus (penicillinase and non-penicillinase producing), Staph. epidermidis, streptococci (excluding enterococci, e.g., Strep. faecalis), E. coli, P. mirabilis, Klebsiella species, Bacteroides species including the B. fragilis group,‡ Clostridium species, Peptococcus species, and Peptostreptococcus species.

Although appropriate culture and susceptibility studies should be performed, therapy may be started while awaiting these results. Cefoxitin is not active in vitro against most strains of Pseudomonas aeruginosa and enterococci (e.g., Strep. faecalis) and many strains of Enterobacter cloacae. Methicillin-resistant staphylococci are almost

uniformly resistant to cefoxitin.

Prevention - Prophylactic use perioperatively (preoperatively, intraoperatively, and postoperatively) in surgical procedures (e.g., vaginal hysterectomy, gastrointestinal surgery) classified as contaminated or potentially contaminated or in patients in whom infection at the operative site would present a serious risk, e.g., prosthetic arthroplasty; intraoperatively (after umbilical cord is clamped) and postoperatively in cesarean section.

MEFOXIN usually should be given 1/2 to 1 hour before the operation, which is sufficient time to achieve effective levels in the wound during the procedure. Prophylactic administration should usually be stopped within 24 hours since continuing administration of any antibiotic increases the possibility of adverse reactions but, in the majority of surgical procedures, does not reduce the incidence of subsequent infection. However, in patients undergoing prosthetic arthroplasty, it is recommended that MEFOXIN be continued for 72 hours after the surgical procedure. If there are signs of infection, specimens for culture should be obtained for the identification of the causative organism so that appropriate therapy may be instituted.

.Contraindications: Previous hypersensitivity to cefoxitin and the

cephalosporin group of antibiotics.

Warnings: BEFORE THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN, CEPHALOSPORINS, PENICILLINS, OR

OTHER DRUGS. GIVE WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFOXITIN OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPH-RINE AND OTHER EMERGENCY MEASURES.

Precautions: The total daily dose should be reduced in patients with transient or persistent reduction of urinary output due to renal insufficiency because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses. As with other antibiotics, prolonged use may result in overgrowth of nonsusceptible organisms; repeated evaluation of the patient's condition is essential. If superinfection occurs, take appropriate measures. Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Interference with Laboratory Tests — As with cephalothin, high concen-

trations (>100 mcg/ml) may interfere with measurement of serum and urine creatinine levels by the Jaffé reaction and produce false increases of modest degree in creatinine levels reported; serum samples should not be analyzed for creatinine if withdrawn within 2 hours of cefoxitin administration. A false-positive reaction for glucose in urine has been observed with CLINITEST<sup>§</sup> reagent tablets.

Pregnancy—In women of childbearing potential, weigh anticipated benefit against possible risks.

Nursing Mothers - Cefoxitin is excreted in human milk in low concentrations

Infants and Children - Safety and efficacy in infants from birth to three months have not yet been established. In children three months and older, higher doses have been associated with increased incidence of eosinophilia and elevated SGOT.

Adverse Reactions: The most common adverse reactions have been local reactions following intravenous or intramuscular injection. Other adverse reactions have been encountered infrequently. Local Reactions — Thrombophlebitis with intravenous administration; pain, induration, and tenderness after intramuscular injections. Allergic Reactions - Rash, pruritus, eosinophilia, fever, and other allergic reactions. Gastrointestinal - Nausea, vomiting, and diarrhea. Blood-Transient eosinophilia, leukopenia, neutropenia, and hemolytic anemia; a positive direct Coombs test may develop in some individuals, espe cially those with azotemia. Liver Function — Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase. Renal Function — Elevations in serum creatinine and/or blood urea nitrogen levels.

Note: In group A beta-hemolytic streptococcal infections, therapy should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated. Intramuscular injections should be well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel. The total daily dosage in infants and children should not exceed 12 grams.

How Supplied: Sterile cefoxitin sodium in vials and infusion bottles containing 1 gram or 2 grams cefoxitin equivalent.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, PA 19486

DOHME

‡B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus Registered trademark of Ames Company. Division of Miles Laboratories, Inc.

#### American Journal of Obstetrics and Gynecology

Copyright © 1980 by The C. V. Mosby Company

Editors

John I. Brewer, Editor in Chief 710 North Fairbanks Court, Chicago, Illinois 60611

Frederick P. Zuspan, Editor

The Ohio State University, 410 W. 10th Ave., Columbus, Ohio 43210

#### Information for authors

Submission of contributions. Manuscripts should in general be sent to a particular Editor according to the following plan: If it is from the southeastern quadrant of the United States or from Canada, or if it has been presented before one of the official sponsoring societies, to Dr. Brewer; if from the northeastern quadrant (including Ohio), or if it is a Clinical Opinion or a Letter to the Editors, to Dr. Zuspan; if from the north central states, any of the United States west of the Mississippi, Hawaii, Alaska, or abroad, to Dr. Quilligan.

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following written statement, signed by one author: "The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C. V. Mosby Company in the event the work is published. The undersigned author warrants that the article is original, is not under consideration by another journal, and has not been previously published. I sign for and accept responsibility for releasing this material on behalf of any and all co-authors." Authors will be consulted, when possible, regarding republication of their material.

All articles published in this JOURNAL must be contributed to it exclusively. Articles previously published in another language are not acceptable.

It is assumed by the Editors that articles emanating from a particular institution are submitted with the approval of the requisite authority.

Articles dealing with human experimentation cannot be accepted unless the experiment was approved by the author's local Human Experimentation Committee.

Statements and opinions expressed in the articles and communications herein are those of the author(s) and not necessarily those of the Editor(s) or Publisher and the Editor(s) and Publisher disclaim any responsibility or liability for such material. Neither the Editor(s) nor the Publisher guarantee, warrant, or endorse any product or service advertised in this publication, nor do they guarantee any claim made by the manufacturer of such product or service.

Manuscripts. Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. The original and one copy of the manuscript are required. References should be placed at the end of the article. They should include name of author(s), article title, name of periodical, volume, page, and year. Name of periodical should conform to that shown in latest List of Journals Indexed in Index Medicus. For reference style see current issue of JOURNAL. Authors are encouraged to limit references to 16, except for Communications in Brief, limited to 2, Current Investigation and Clinical Opinion, limited to 6, and Current Developments, for which there is no limit. Illustrations accompanying manuscripts should be numbered, provided with suitable

#### E. J. Quilligan, Editor

University of California, Irvine, Medical Center, Department of Obstetrics and Gynecology, Building 16, 101 City Dr. S., Orange, California 92668

Albert B. Gerbie, Associate Editor
710 North Fairbanks Court, Chicago, Illinois 60611

legends, and marked lightly on the back with the author's name. Authors should indicate on the manuscript the approximate position of tables and text figures.

Tables should be typed on separate sheets of paper, not in the text, with one table to a page. They should be numbered in sequence and each must be referred to at an appropriate point in the text. Captions of the tables should be brief, yet indicate clearly the purpose or content of each table. Rows and columns in the table should precisely define the nature of the data in each. Abbreviations in tables should be used as little as possible and if abbreviations are used they should be explained in a footnote to the table.

An abstract of 50 to 150 words, to be published as an introduction, should accompany each manuscript and should be typed on a separate sheet of paper.

A footnote should be included which gives the name and complete mailing address of the person to whom reprint requests and correspondence should be sent.

A Guide to Writing for the American Journal of Obstetrics and Gynecology may be obtained from the Publisher on request.

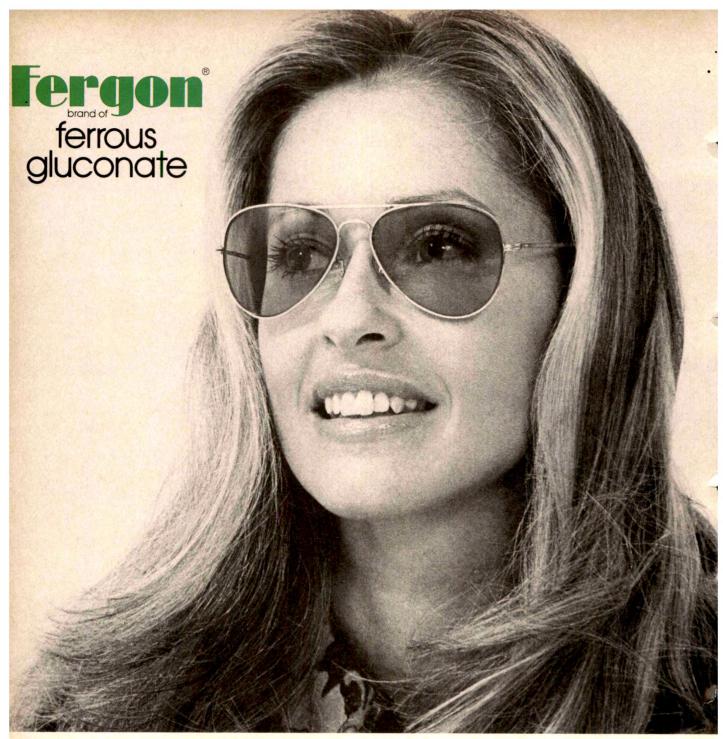
Illustrations. A reasonable number of halftone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the Editors for color plates, elaborate tables, or extra illustrations. Original drawings or graphs should be drawn with black India ink. Typewritten or freehand lettering is not acceptable. All lettering must be done professionally. Do not send original art work, x-ray films, or ECG tracings. Glossy print photographs are preferred, for good black and white contrast is essential. Illustrations will be returned only if requested by the author.

Announcements. Announcements of meetings must be received by Dr. Brewer at least 2½ months prior to the time of the meeting. Such announcements should concern major meetings and other significant activities. Announcements of symposia or seminars for which fees are charged are not published in the scientific pages of the JOURNAL but may be submitted for paid advertisements, if desired.

Letters to the Editors. A brief Letter to the Editors commenting upon some article which has appeared in the JOURNAL will be considered for publication. The writer of the original article will have an opportunity to reply to unfavorable comments. A brief case presentation of special interest in the form of a Letter to the Editors will also be considered for publication. All such letters should be sent to Dr. Zuspan.

**Books.** Books received will be listed in the JOURNAL. They should be sent to Dr. Gerbie.

Reprints. Reprints of articles must be ordered from the Publishers, The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141, who will send their schedule of prices. Individual reprints of an article must be obtained through the author.



## When she needs replacement therapy for hypochromic anemia of pregnancy, because it provides the three advantage.

provides the three advan-

tages you want in oral iron therapy: excellent tolerance • proven effectiveness economy.

Fergon encourages a rapid hemoglobin response and it is well tolerated and non-constipating in the great majority of patients. It is soluble throughout the entire pH range of the g.i. tract and is available for absorption at the upper intestinal site of maximum absorption.

Each tablet contains 320 mg (5 grains) ferrous gluconate equal to approximately 36 mg ferrous iron. Dosage: Adults, one or two tablets three times daily; Children, 6-12 years, one tablet one to three times daily, as directed by the physician. Supplied: Bottles of 100 and 1000. Each capsule contains 435 mg ferrous gluconate equal to approximately 50 mg ferrous iron. Dosage: Adults, one daily or as directed; Children, as directed. Supplied: 3ottles of 30.



#### American Journal of Obstetrics and Gynecology

volume 138 number 2 September 15, 1980

#### **CLINICAL OPINION**

This section reports opinion on the handling of clinical situations, i.e., the clinical diagnosis and management of certain disease entities. Papers should range from eight to twenty typed pages, including illustrations, tables, and figures which clarify the author's management. References are limited to sixteen citations. Mail to Frederick P. Zuspan, M.D., Editor.

### Technical progress in pelvic surgery via operative laparoscopy

K. SEMM

L. METTLER

Kiel, Germany

The development of an optimal set of instruments for perfect grasping, cutting, sucking, and ligating and of a new system to perform hemostasis by endocoagulation through a trocar sheath 7 to 11 mm in diameter permits effective laparoscopic surgery. A total of 2,000 operative laparoscopies were performed safely between 1973 and 1976. Since 1977, laparoscopic surgery has been extended to the following procedures: myomectomy isubserous), adnexectomy, ovarian cyst resection, removal of a cystoma, and tubectomy in cases of tubal pregnancy. In 82 such cases, no intraoperative or postoperative complications occurred. The normal postsurgical healing procedure has been checked during 18 second-look laparoscocies and two consecutive laparotomies. These technical advances have opened up a new era of graecologic surgery based on operative laparoscopy. (Am. J. Obstet. Gynecol. 138:121, 1580.)

MANY GYNECOLOGIC and general surgical laparcscopic procedures can now be performed with the help

From the Department of Obstetrics and Gynecology of the University of Kiel and Midwifery School.

Support from WISAP, Germany, and Storz, Germany, & acknowledged.

Reprint requests: Prof. Dr. K. Semm, Department of Obstetrics and Gynecology, University of Kiel, School of Medicine, Kiel, Germany.

of a new endocoagulation technique to ensure better hemostasis. With this technique the temperature of boiling water (100° C) is used to achieve hemostasis resulting from protein coagulation (Fig. 1). During the operative laparoscopy, if more widespread bleeding occurs, the Roeder\* loop† can be used for one-handed

\*H. Roeder (1866-1918) recommended a special loop for tonsillectomy in children.

†Made by Ethicon.



Fig. 1. Principle of the endocoagulation technique. The tissue (e.g., the fallopian tube) is grasped between two branches (e.g., the crocodile forceps). The lower branch is heated to 110° to 120° C and the enclosed proteins coagulate under this condition. This procedure produces optimal hemostasis without burning or carbonization of the tissue.

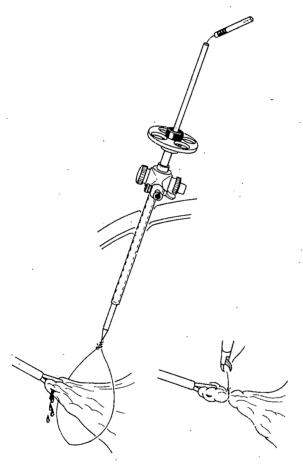


Fig. 2. Demonstration of the Roeder loop to ligate intraabdominal bleeding tissue. After the loop is introduced through the loop applicator, according to Semm, a forceps is used to grasp the bleeding tissue through the loop. After the loop is tied, the suture is cut with the hooked, formed scissors.

ligation (Fig. 2) through a trocar sheath 5 mm in diameter.<sup>1</sup>

In 1962, a thermocoagulation system (coagulating at 90° to 100° C) was developed for the treatment of benign lesions of the uterine cervix.<sup>2</sup> Since 1973, the coagulation technique has been applied in laparoscopic surgery. At first this was only used for tubal coagulation, whether transuterine<sup>3</sup> or transabdominal,<sup>4</sup> but af-

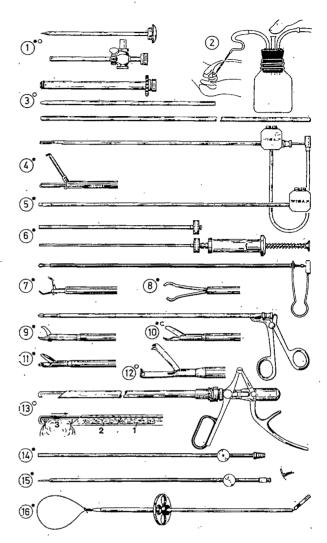


Fig. 3. Set of instruments to be used according to Semm for endoscopic intra-abdominal surgery. 1: 5.5 mm diameter + 11 mm diameter conic trocar for the trocar sheath with trumpet valve. 2: Suction bottle for collecting aspirate. 3: Dilation set from 6 to 11 mm diameter trocar sheath (for photographic reasons or for the introduction of larger instruments. 4: Crocodile forceps for endocoagulation with or without the water-cooling system. 5: Point coagulator for endocoagulation. 6: Suction palapator. 7: and 8: Atraumatic forceps and dilator for the ampulla. 9: Hooked, formed scissors or tube scissors. 10: Broad scissors. 11: Biopsy forceps with grasping teeth. 12: Grasping forceps for a myoma, ovary, etc. 13: Tissue punch with receptaculum. 14: Suction and rinsing cannula. 15: Puncture needle. 16: Loop applicator for Roeder ligation.

terward also for the coagulation of endometriotic foci ir. the lower pelvis and lesions in the ovary after biopsy. In operative sterilizations this technique is now used for lysis of adhesions, the ovaries, and the tubes and for salpingoplasty and/or salpingostomy via laparoscopy.<sup>5, 6</sup>

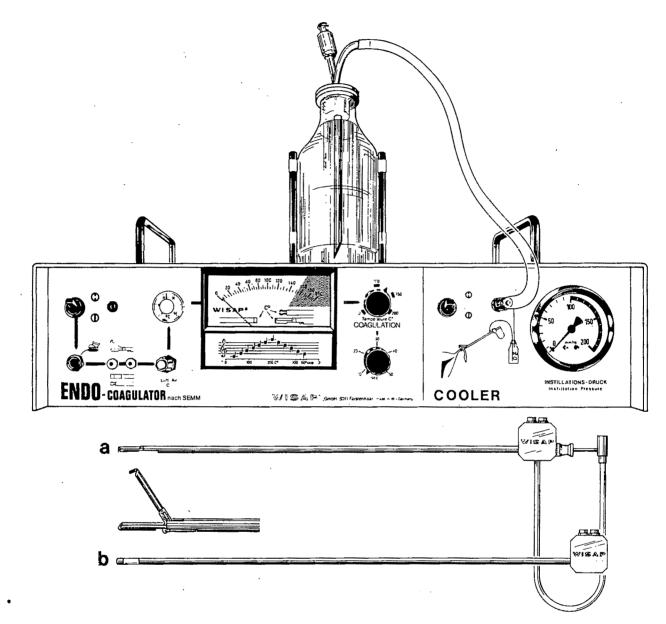


Fig. 4. Endo-Coagulator with cooling system developed by Semm for laparoscopic surgery to monitor the blood coagulation at 100° C, with the crocodile forceps (a) and the point coagulator (b).

Destructive heat was used in 61% of 3,900 laparoscopies performed during 1971 to 1977. Since the complications of laparoscopy did not increase, in spite of the increase in numbers of surgical therapeutic procedures since 1973 (the beginning of the use of endocoagulation), the technique was extended to larger endoscopic-surgical procedures, such as ovariectomy, myomectomy, partial resection of the ovary, cystertomy, and tubectomy.

#### Material and methods

Instruments. The basis of advances in laparoscopic surgery was the development of handy and useful instruments (Fig. 3) for grasping, cutting, and sucking. The tissue punch allows the removal of bigger organs, such as ovaries, cyst walls, and myomas, by morcellation. Another advance is a new model of the Semm Pneu-Automatic device which is electronically controlled and replaces the peritoneal gas in a secure manner during surgical procedures.

The Endo-Coagulator (Fig. 4) is a major factor in extended laparoscopic surgery. It has been tested and proved in 3,000 cases. The coagulation procedure guarantees sufficient hemostasis if the grasped tissue is heated to 100° to 120° C for 20 seconds. For the grasping of tissue the crocodile forceps can be used, and for

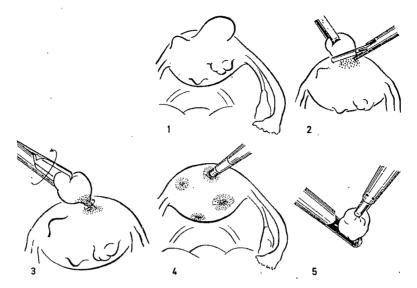


Fig. 5. Schematic demonstration of pelviscopic myom ectomy. 1: Small subserous myomas are in situ. 2: The myoma is pulled and at the same timing the stem is coagulated with the crocodile forceps at 120° C. 3: The myoma is twisted and removed. 4: Hemostasis of the lesion on the surface of the uterus is obtained with the point coagulator at 120° C. 5: The fibromas are morcellated with the tissue punch.

more precise hemostasis the point coagulator is recommended.

Surgical laparoscopy can only be performed with the use of two or more abdominal portals (6 mm in diameter for the instruments and 6 to 8 mm in diameter for the eyepiece). The so-called "surgical endoscope" is unsuitable for endoscopic surgery since stereoscopic investigation of the organs is impossible.

Technique of myomectomy. Myomas can be removed as shown in Fig. 5. Generally two punctures are sufficient for the removal of small myomas. For larger ones puncture with an 11 mm trocar is necessary for insertion of the tissue punch used for morcellation (see Fig. 3).

If a large, pedunculated myoma has a small stem, it is not morcellated but is pushed down through a colpotomy posteriorly into the vagina with the end of the suction needle.

The hemostasis following myomectomy must be performed at 100° to 120° C with constant slight rotation of the point coagulator. If the proteins are coagulated, the bleeding stops. To date there has been no evidence of subsequent adhesion of the bowel to the operative site. This is because no thrombokinase, fibrocytes, or histiocytes are released from the coagulated wound and the healing procedure after the 100° C coagulation is quite different from that of a burning wound induced by high-frequency current coagulation.

**Ovariectomy.** Four punctures are necessary, one in the umbilicus for the eyepiece, one on the left and one

on the right over the pubic hair margin with 6 mm trocars, and one in the midline with an 11 mm trocar.

When the trocars are inserted, a ligation loop is introduced on the side of the ovary to be removed (Fig. 6). The large forceps in the center position must be introduced through the loop to grasp and pull the ovary through. After the suture loop is put over the ovary, the loop is ligated by traction. The assistance of an atraumatic forceps is sometimes necessary to guide the catgut suture over the ovary. Three ligatures are placed on the ovarian pedicle. The ovary is cut loose with the aid of the hooked, formed scissors. A small stump above the three ligatures remains. The ovary is taken out by morcellation with the tissue punch and the ligated tissue stump is then coagulated for 20 seconds at 120° C with the point coagulator in order to prevent adhesions.

Andexectomy. The fallopian tube is sometimes adherent to the ovary because of previous operative procedures or infections. In such cases the ligation loop can be conducted behind the ampulla in order to ligate the infundibulopelvic ligament, mesosalpinx, tube, and uterosacral ligament (Fig. 7).

Removal of a pregnant fallopian tube. Laparoscopy allows the detection of tubal pregnancies at an early stage. If a conservative surgical treatment via laparotomy seems to be inappropriate for the case, the tube can be grasped and ligated in a method similar to that used in an ovariectomy (Fig. 8) via laparoscopy.

Resection of ovarian cysts. Ovarian cysts up to the

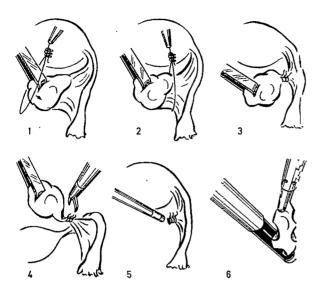


Fig. 6. Scheme of laparoscopic ovariectomy. 1: The ovary is grasped with the large forceps (11 mm diameter) and passed through the Roeder loop (Ethi-Ligator). 2: The loop is placed around the ovarian ligament for ligation. 3: The ovarian lizament is ligated three times for safety reasons. 4: Under slig t retraction the ovary is dissected with the hocked, formed sc 1sors. 5: The remaining tissue stump must be coagulated with the point coagulator for prevention of later adhesions. 6: The ovary is morcellated with the tissue punch.

size of an orange may be evacuated (Fig. 9). The cyst wall is resected with the hooked, formed scissors and removed through the trocar sheath. The cyst wall borders on the ovary and the remaining crater must be coagulated with the crocodile forceps and/or the point coagulator (120° to 140° C, 20 to 60 seconds). If no ovarian tissue remains, the ovary can be removed totally (see Fig. 6).

Cyst resection is surprisingly effective in the treatment of ovarian endometriotic cysts. These can be removed in the same manner as other ovarian cysts with conservation of a residual part of the ovary. A 6-month treatment with gestagens or antigonadotropin follows. In patients undergoing a second-look laparoscopy 6 to 9 months later, nearly normal internal genital organs can be observed.

General procedure for laparoscopic surgery. In patients undergoing resection of ovarian cysts, especially endometriotic cysts, bleeding cannot be avoided. With the help of the Aqua-Purator (see Fig. 10), the bload can be sucked off very easily through the 4 mm suction cannula. The instillation of 500 ml of saline once or twice, followed by reaspiration, cleans the lower pelvis.

After extended cutting of adhesions a final instillation of 500 ml of saline solution with 500 mg of certisone prevents the formation of new adhesions.

The patient can be mobilized after termination of the

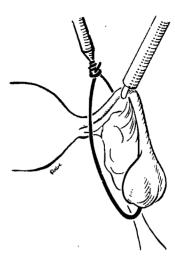


Fig. 7. If the ovary is connected to the tube by adhesions, the ligation can be performed around the entire adnexa. The pelvic infundibulum, tube, ovary, and mesosalpinx are ligated.

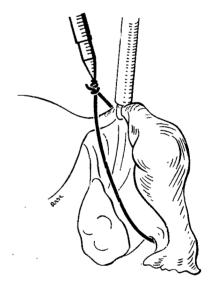


Fig. 8. In tubal pregnancy the ligation should include only the tube and the tuboovarian ligament, e.g., the mesovarium.

anesthesia, but she must remain in the recovery room. She may start to drink and/or to eat if she desires, because no paralysis of the bowel is provoked (in contrast to the situation following a laparotomy).

#### Comment

After performing more than 2,000 cases of simple operative laparoscopy without bleeding complications, the following, more extreme procedures have now been performed: 14 ovariectomies with removal of both ovaries in cases of cancer of the breast: 9 adnexectomies (same indication but with tubal adherence); 4 adnexectomies 4 to 10 years after abdominal hysterec-

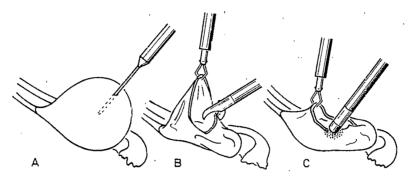


Fig. 9. First the fluid of the ovarian cyst is sucked off. Under traction the tissue of the cyst is cut with the hooked, formed scissors, and the lesion is coagulated with the point coagulator and/or the crocodile forceps.

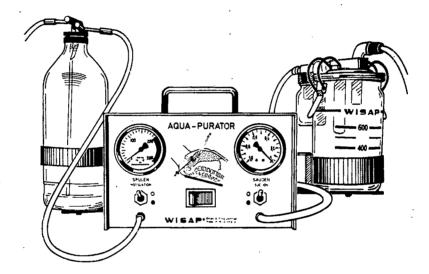


Fig. 10. The Aqua-Purator facilitates the purification of the minor pelvis by instillation of saline solution and consecutive sucking of the fluid.

tomy; 3 adnexectomies 4 to 6 years after vaginal hysterectomy; 5 ovariectomies for ovarian cyst formation in women over 50 years; 2 adnexectomies in cases of large, simple, unilocular serosal cysts of the ovary; 28 ovarian cyst resections, 14 endometriotic cyst resections; 2 tubectomies in an early stage of tubal pregnancy.

For all patients the physiologic stress was similar to that of a sterilization procedure with full anesthesia. All patients had five postoperative days under clinical control without complications. The opportunity has arisen to assess these operative laparoscopies so far in 18 cases on the occasion of a second-look laparoscopy. In cases of myomectomy the minor pelvis did not show any adhesions to the uterine wall; in the cases of ovarian cyst resection the ovary was found to be normal, and in cases of an ovariectomy or adnexectomy the operative site looked normal and no adhesions had formed.

According to Palmer,7. 8 safety in laparoscopy is a

prerequisite as in any other operative technique. The experiences of other laparoscopic surgeons<sup>9–16</sup> and of our group <sup>17, 18</sup> demonstrate, however, that the described operative laparoscopy applied by the expert who uses all known safety methods<sup>13</sup> does not indicate an increased risk for the patients. On the contrary, for the patient operative laparoscopy involves a shorter hospital stay, less physical stress, and the possibility of subsequent laparotomy in unsuccessful cases treated by laparoscopy.

A prerequisite for all laparoscopic surgery is the presence of an optimal and complete set of instruments and special training in their use. Laparoscopy may be an easy procedure, but operative laparoscopy requires a special knowledge. However, such requirements should not hinder gynecologists from entering this new era of laparoscopic surgery.

#### REFERENCES

- Semm, K.: Endoskopische Ligaturen mit Hilfe der Schlingen-Unterbindung-Ethibinder Aus der Serie in Dienste der Chirurgie, Hamburg, 1978, Ethicon GMBH.
- Semm, K.: New apparatus for the "cold-coagulation" of benign cervical lesions, Am. J. Obstet. Gynecol. 95:963, 1966.
- Semm, K.: Transabdominale oder transvaginale Eileitersterilisation mit einer neuen Koagulationszange, Endoscopy 6:40, 1974.
- Semm, K.: Tubal sterilization finally with cauterization otemporary with ligation via pelviscopy, in Philipps, J., and Keith, K., editors: Gynecological Laparoscopy—Principles and Techniques, Miami, Florida, 1974, Symposia Specialists, pp. 337-359.
- 5. Semm, K.: The technique of gynecological pelviscopy in human reproduction, in Campos Da Paz, A., Hasegawa, T., Notake, M. P., and Hayashi, M., editors: Human Reproduction, Kyoto, 1974, Igaku Shoin, pp. 101-112.
- Semm, K.: Endocoagulation: A new field of endoscopic surgery, J. Reprod. Med. 16:195, 1976.
- 7. Palmer, R.: Safety in laparoscopy, J. Reprod. Med. 13:1, 1974.
- 8. Palmer, R.: Le Explorations Fontionelles Gynecologiques, Paris, 1975, Masson et Cie.
- Steptoe, P. C.: Recent advances in surgical methods cf control of fertility and infertility, Br. Med. Bull. 26:60, 1970.

- Neuwirth, R. S.: Recent experience with diagnostic and surgical laparoscopy, Am. J. Obstet. Gynecol. 106:119, 1970.
- 11. Roland, M. D.: Tuboplasty in 130 patients. Improved results due to stents and preoperative endoscopy, Obstet. Gynecol. 39:57, 1972.
- Berci, G., Adler, D., Brooks, P., Pasternak, A., and Hassler, G.: The importance of instrumentation and documentation in gynecological laparoscopy, J. Reprod. Med. 10:267, 1973.
- Rioux, J. E.: Operative laparoscopy, J. Reprod. Med. 10:249, 1973.
- Hulka, J. F., Soderstrom, R. M., Cobson, S. L., and Brooks, P. G.: Complications committee of the American Association of Gynecological Laparoscopists, J. Reprod. Med. 10:301, 1973.
- 15. Cohen, M. R.: Surgical laparoscopy in infertility, J. Reprod. Med. 15:41, 1975.
- Philipps, J. M.: Laparoscopy, Baltimore, 1976, The Williams & Wilkins Company.
- Semm, K.: Atlas of Gynecologic Laparoscopy and Hysteroscopy. English: Philadelphia, 1977, W. B. Saunders Co., German: Stuttgart, 1976, F. K. Schattauer Verlag; French: Paris, 1977, Masson et Cie; Portugese: Sao Paulo, 1977, Ed. Manola Ltd.; Spain: Barcelona, 1977, Toray Masson S. A.
- Mettler, L., Giesel, H., and Semm, K.: Extreme Verläufe der Routine-Pelviskopie, Fortschr. Med. 33:1657, 1978.

#### Gynecologic Pathology for the Clinician

A postgraduate winter review course, "Gynecologic Pathology for the Clinician," will be held February 10-13, 1981, at Big Sky, Montana. This course is offered by the Department of Obstetrics and Gynecology of the University of Vermont and the Departments of Pathology and Obstetrics and Gynecology of the Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec, Canada. It is designed for both the clinician and the pathologist with emphasis on current pathogenetic and diagnostic concepts of gynecologic disorders and advances in their outpatient diagnosis. The faculty includes: J. Belinson, M.D., A. Ferenczy, M.D., M. M. Gelfand, M.D., R. M. Richart, M.D., Stanley Robboy, M.D., and Donald Woodruff, M.D. This course is approved for 22 credit hours in the American Medical Association, Category I, and for 22 cognates by the American College of Obstetricians and Gynecologists.

For application contact: Dr. A. Ferenczy, Department of Pathology, The Sir Mortimer B. Davis Jewish General Hospital, 3755 Côte Ste. Catherine Road, Montreal, Quebec, Canada H3T 1E2.

#### **GYNECOLOGY**

### The treatment of endometriosis at laparoscopy for infertility

JOAN M. SULEWSKI, M.D.
FREDERICK D. CURCIO, M.D.
CARL BRONITSKY, M.D.\*
VINCENT G. STENGER, M.D.\*\*
Hershey, Pennsylvania

Endometriosis is found in some infertile women, and treatment by laparotomy and/or hormonal therapy is associated with subsequent pregnancy. In this study, 100 consecutive patients with mild/moderate endometriosis were treated at laparoscopy. Forty of these women achieved a pregnancy within 37 months postoperatively; 73% of these pregnancies occurred within 6 months, and 88% within 12 months of operation. Although this pregnancy rate is similar to rates obtained after treatment by laparotomy and/or hormonal therapy, the pregnancies in this study population occurred significantly earlier than after laparotomy or combined therapy. The age of the women, duration of infertility, parity; extent of endometriosis, or presence of additional treatable factors of infertility did not affect the pregnancy rate. There was no significant morbidity, and the procedure can be performed on an outpatient basis with local anesthesia. Laparoscopy offers a practicable alternative for the treatment of mild/moderate endometriosis in infertile women. (Am. J. Obstet. Gynecol. 138:128, 1980.)

From the Division of Endocrinology and Infertility, Department of Obstetrics and Gynecology, The Pennsylvania State University College of Medicine, The Milton S. Hershey Medical Center.

Presented at the Fourth International Congress of Gynecologic Endoscopy of the American Association of Gynecologic Laparoscopists, November 4-9, 1979, Las Vegas, Nevada; and in part at the American Fertility Society Thirty-Fifth Annual Meeting, February 3-7, 1979, San Francisco, California.

Received for publication January 3, 1980.

•Revised March 17, 1980.

Accepted March 28, 1980.

Reprint requests: Joan M. Sulewski, M.D., Division of Endocrinology and Infertility, Department of Obstetrics and Gynecology, The Milton S. Hershey Medical Center, Hershey, Pennsylvania 17033.

\*Present address: Department of Obstetrics and Gynecology, Harrisburg Hospital, Harrisburg, Pennsylvania 1710!.

\*\*Present address: 1801 Arlington St., Sarasota, Florida 33579. DURING a routine evaluation for infertility, endometriosis may be asymptomatic and undetected on pelvic examination but may be found by endoscopy. Although the mechanism by which endometriosis interferes with conception is unknown, an average expected pregnancy rate of 40% to 50%1 has been reported with the treatment of endometriosis by hormonal regimens or conservative operation by laparotomy. An alternative approach to surgical therapy may be at the time of diagnostic laparoscopy when mild or moderate2 endometriosis in infertile women can be treated by fulguration of endometrial implants and lysis of adhesions.3, 4 The number of pregnancies subsequent to laparoscopic treatment of endometriosis in infertile women indicates that this is a practicable alternative means of therapy.

#### Material and methods

Procedure and instruments. At laparoscopy, 100 consecutive infertile women who had mild or moderate

pelvic endometriosis were treated by fulgurating the endometrial implants and lysing any adhesions. The procedure was accomplished with unipolar cautery at setting No. 3 on the Martin Elektrotcm 120 (Elmed Incorporated, Addison, Illinois) through a 10-mm, single-puncture Palmer-Jacobs operating laparoscope with the use of 3-mm grasping forceps and hook scissors (Richard Wolf Medical Instruments Corporation, Rosemont, Illinois). The operation was performed with the patient under local or general endotracheal anesthesia either as an outpatient or during a 24 to 48 hour hospitalization. At the time of operation, a detailed description and a sketch of the pelvic firdings were recorded. Endometriosis was diagnosed by the characteristic appearance of bluish-black stipp ed areas on the peritoneal or ovarian surfaces.

After the pelvic area had been completely inspected, treatment was initiated only if all sites of endometriosis were considered to be safely accessible through the laparoscope. Superficial, scattered implants of endometriosis on the ovaries, and peritoneal surfaces covering the uterus, uterine ligaments, and anterior or posterior cul de sac were fulgurated. Endometriomas which were clearly superficial and less than 1 cm in size also were fulgurated. Minimal, thin, filmy periovarian or peritubular adhesions were lysed. The presence of massive or dense adhesions, endometriomas that were deep or of uncertain size, thickened, deep endometrial implants, and implants over the fallopian tubes, ureter, or bowel precluded laparoscopic treatment.

Patients. All patients were evaluated and treated at the Milton S. Hershey Medical Center during a 4-year period, 1974 to 1978. Prior to laparoscopy, the 100 women and their male partners completed an infertility evaluation that included a semen analysis, a post-coital cervical mucus test, a hysterosalpingogram, and a timed endometrial biopsy. All of the women had patent fallopian tubes. None was treated for 1 to 2 cm subserosal uterine fibromas or a bicornuate uterus. Patients who underwent donor insemination or ovulation induction therapy were treated for at least 6 months prior to the laparoscopy, and the treatment was continued after the operation.

#### Results

Pregrancies. Forty of the 100 consecutive infertile women who were treated for mild or moderate endometriosis at laparoscopy achieved a pregnancy within 37 months after the operation. Seventy-three percent of the pregnancies occurred within the first 6 months after the operation, and 88%, within the first year. Cumulative pregnancy rates in women with mild or moderate endometriosis were similar (Fig. 1). The 40

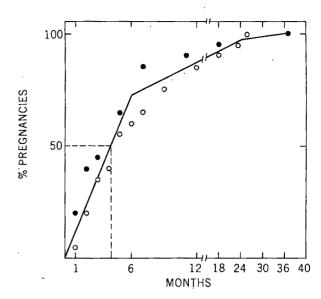


Fig. 1. The cumulative rate of conception (—) in 40 women after laparoscopic treatment of mild endometriosis (o), N = 20, and moderate endometriosis (•), N = 20.

women had a total of 50 pregnancies, including one twin pregnancy, 38 term pregnancies, eight spontaneous abortions, and three ectopic pregnancies. At least one liveborn infant was delivered of 35 of the women.

Effect of age and degree of endometriosis on pregnancy rate. The pregnancy rates were not significantly different in any age group or in the women with mild or moderate endometriosis. Twenty of the 42 women with mild endometriosis, and 20 of the 58 women with moderate endometriosis achieved a pregnancy. The average age of the women was 28.6 years. Among the women with mild endometriosis, the mean  $\pm$  SD age was 27.8  $\pm$  2.28 years (range, 21 to 33 years), whereas the mean  $\pm$  SD age among the women with moderate endometriosis was 29.2  $\pm$  3.68 years (range, 23 to 39 years) (p < 0.05).

Effect of parity and duration of infertility on pregnancy rate. Parity did not affect the pregnancy rate. Twelve of the 28 parous women and 28 of the 72 nulliparous women achieved a pregnancy after laparoscopic treatment of endometriosis. Moderate endometriosis was found in 75% of the parous women and in 51% of the nulliparous women, but this difference was not significant.

The average duration of infertility among the women was 4 years (range, 1 to 11 years). Twenty of the 50 women with infertility from 1 to 3 years achieved a pregnancy, and 20 of the 50 women with infertility for more than 3 years became pregnant. There was no significant difference in the mean  $\pm$  SD duration of infertility among the women with mild endometriosis,  $3.8 \pm 2.51$  years, or with moderate endometriosis,

Table I. A comparison of pregnancy rates in infertile women treated for mild/moderate endometriosis

Treatment	Pregnant patients/ total potients	No. of pregnancies at 6 moltotal pregnancies	No. of pregnancie at 12 mo/ total pregnancies
None <sup>2,7,8</sup>	60/133 (45%) <sup>a, b</sup>		10/11 (91%)7
Laparoscopy		•	
This study	40/100* (40%)	29/40 (73%)	35/40 (88%)
Hasson <sup>3</sup>	6/8 (75%) <sup>a, c</sup>	5/6 (83%)	6/6 (100%)
Eward <sup>4</sup>	14/25 (56%) <sup>f</sup>	(average pregnancy 3.6 mo)	14/14 (100%)
Total .	60/133 (45%)a.c.f	34/46 (74%)	55/60 (92%)
Laparotomy			, ;
Buttram <sup>5</sup>	89/138† (64%) <sup>a</sup>	43/89‡ (48%)	73/89 (82%)
Acosta et al <sup>2</sup>	36/68 (53%) <sup>a</sup>	-	35/49. (71%)e
Sadigh et al.9	17/23§ (74%)a,d	···	11/17 (65%)
Garcia and David <sup>7</sup>	9/22 (40%) <sup>a</sup>	morning.	<u></u>
Hammond et al.10	5/8 (63%) <sup>a</sup>	taverage pregnancy, 20 mo)	
Total	156/259† (60%)*	43/89‡ (48%)	119/155 (77%) <sup>e</sup>
Hormonal		, , , ,	, , ,
Danazol <sup>11</sup>	36/73 (49%) <sup>a</sup>	23/39 (59%) <sup>e</sup>	30/39 (77%)°
Medroxyprogesterone <sup>12</sup>	11/20 (55%)		
Methyltestosterone <sup>6,10</sup>	13/73§ (18%)ª	taverage pregnancy, 6.4 mo)6	
Estrogen and progestin <sup>13</sup>	6/19 (32%) <sup>a</sup>		4/7 (57%)°
Estrogen and progestin <sup>1</sup>	94/186 (51%)		<u></u>
Total	163/382 (43%) <sup>a</sup>	23/39 (59%) <sup>e</sup>	34/46 (74%)e
Laparotomy and hormonal		•	
Estrogen and progestin <sup>13</sup>	7/19 (37%)ª	latinatory.	2/8† (25%)°
Methyltestosterone <sup>10</sup>	2/6 (33%) <sup>a</sup>	distributions.	
Total	9/25 (36%) <sup>a</sup>	Address:	2/8† (25%)e

<sup>\*50%</sup> of pregnancies, 4.1 mo; average pregnancy, 6.9 mo.

 $4.2 \pm 2.37$  years, or among those who achieved pregnancy,  $4.0 \pm 2.50$  years, or who did not,  $4.1 \pm 2.35$  years.

Effect of additional infertility factors; follow-up. There were 20 women who became pregnant among the 43 women with additional factors contributing to infertility. Pregnancies occurred in 13 of 30 women with male factors, two of the four women with ovulatory factors, and five of the nine women with a combination of uterine, male, or ovulatory factors. The pregnancy rates did not differ significantly from those of the women without additional factors.

Within an average of 5.4 months (range, 1 to 11 months) after the laparoscopy, 26 women were either lost to follow-up, had adopted a child and were not interested in an immediate pregnancy, or had discontinued treatment of the additional factors which were contributing to their infertility. This group included four women with minimal endometriosis and eight

women with moderate endometriosis who had no additional factors for infertility; two women with minimal endometriosis and three with moderate endometriosis who had either a male, uterine, or ovulatory factor, or a combination of factors, associated with their infertility; and five women with minimal endometriosis and four with moderate endometriosis who discontinued donor insemination. The average follow-up among the other 34 women who did not become pregnant was 17.7 months (range, 12 to 48 months). Two of these women underwent laparoscopy again and were found to have a recurrence of endometriosis 12 and 17 months after the initial operation.

Dysmenorrhea. Forty-three women, 18 with mild endometriosis and 25 with moderate endometriosis, complained of dysmenorrhea prior to the laparoscopy. Postoperatively, this symptom was alleviated in 29 women, and 13 of them became pregnant; in four women the symptom was not allayed until after preg-

<sup>†</sup>Significance compared to this study: p < 0.001.

<sup>‡</sup>Significance compared to this study: p < 0.02.

<sup>§</sup> Significance compared to this study: p < 0.01.

<sup>&</sup>lt;sup>a</sup> = Patients selected from larger group.

h = Mild endometriosis only.

<sup>&</sup>quot; = "Fairly extensive" endometriosis in five patients.

d = Moderate endometriosis only.

e = Includes pregnancies among patients with severe endometriosis.

f = Conjugated estrogens postoperatively to improve cervical mucus and tubal motility.

nancy had occurred; and the other 10 vomen neither became pregnant nor found any relief from their symptom. There was no significant difference in the numbers of women with dysmenorrhez in the groups with mild or moderate endometriosis. In four women, two of whom achieved a pregnancy, mild symptoms recurred within an average of 16.5 months after laparoscopy, but additional treatment was not required.

Hospitalization, anesthesia, morbidity. Early in the study, 16 women were hospitalized for 24 to 48 hours for laparoscopic treatment of their endometriosis. The other 84 women were hospitalized fcr less than 24 hours. Local anesthesia with parenteral analgesia was used in six women who had mild endometriosis and in six women who had moderate endometriosis. The other 88 women chose general endotracheal anesthesia. There was no mortality; the postoperative nausez, vomiting, or pain experienced by a few of the women was treated with antiemetics or mild analgesics. Extended hospitalization or rehospitalization was not required for any of the women as a complication of the laparoscopy.

#### Comment

An overall pregnancy rate of 40% occurred among 100 consecutive infertile women whose mild or mocerate endometriosis was treated at laparoscopy. This pregnancy rate included the 26 women who were either lost to follow-up or no longer were interested in a pregnancy during an average of 5.4 months after operation. Of these pregnancies, 73% occurred within 6 months of the operation, and 88% within the first year, after an average duration of infertility of 4 years. Among the 50 pregnancies that occurred, the numbers of spontaneous abortion (16%) and ectopic pregnancy (6%) are similar to pregnancy outcomes after laparoxomy or hormonal treatment of endometriosis.2.5,6

The pregnancy rate in this study after laparoscop.c treatment of mild or moderate encometriosis was comparable to that in other studies and to that with most other types of therapy (Table I) A significantly lower pregnancy rate is associated with methyltestosterone treatment.6, 10 In some studies5, 9 there was a significantly greater pregnancy rate after conservative operation by laparotomy for mild or moderate endometriosis; however, the pregnancies after laparotomy occurred significantly later than those after laparoscopy. The cumulative pregnancy rates at 12 months after any type of therapy were similar, except for laparotomy, followed by hormonal therapy, which was associated with the lowest cumulative pregnancy rate.

Still unexplained is the variable effect of endome-

triosis on fertility. In some studies, certain women with minimal endometriosis diagnosed at endoscopy<sup>2, 7, 8</sup> were not treated, and the subsequent pregnancy rate was not significantly different from that obtained after laparoscopic treatment (Table I). Our study included three women who had remained infertile after undergoing laparoscopy 1 to 3 years earlier at another institution where endometriosis was diagnosed but not treated because of the minimal extent of the disease. All three achieved a pregnancy within 6 months after laparoscopic treatment of the endometriosis.

As in other studies,5,7 the pregnancy rate was not significantly affected by the age of the patient, duration of infertility, parity, or additional treatable factors which were contributing to the infertility. However, some investigators2, 9 have found that one or more of these factors influenced the pregnancy rate. The extent of endometriosis had no significant correlation with the parity, duration of infertility, or pregnancy rate, but those women with moderate endometriosis were older.

Dysmenorrhea is frequently associated with endometriosis.3, 5, 7, 10, 11 As noted by others,5, 10 the symptom did not correlate with the extent of endometriosis. After laparoscopy, 77% of the 43 women with this complaint either became pregnant or had relief from dysmenorrhea. The number of women who had amelioration of their symptom was comparable to that in other studies that used laparoscopy,3 conservative operation,7 or conservative operation and hormonal therapy.<sup>10</sup> Whenever presacral neurectomy or hormonal therapy is used, almost all women are relieved of their symptom.7. 10-13 However, the symptom tends to recur in approximately one third of women after hormonal treatment is discontinued. 10, 11, 13 Since some women with dysmenorrhea have a greater than normal concentration of prostaglandins in plasma, in menstrual fluid, or in the endometrium, the use of prostaglandin synthetase-inhibiting drugs to decrease the amount of prostaglandins is an alternative means of relieving dysmenorrhea.14. 15

In comparison to laparotomy and/or hormonal therapy, laparoscopic treatment of endometriosis is relatively simple and inexpensive. Hospitalization for the majority (84%) of patients was less than 24 hours, or treatment was on an outpatient basis. Although general anesthesia was preferred by 88% of the women, the procedure could be carried out with local anesthesia in certain patients. A few women who had local anesthesia requested, and were able, to observe the procedure through a fiberoptic extension of the laparoscope.

The flat, superficial peritoneal implants of endometriosis were cauterized through the laparoscope with . unipolar instruments rather than being grasped between bipolar forceps; a second incision which others<sup>3, 4</sup> use for the instruments was not essential. Although the potential for serious complications, such as ureteral burns, <sup>16</sup> may be increased by unipolar diathermy, morbidity in this study was confined to the minor discomforts associated with laparoscopy, namely, nausea, vomiting, and shoulder pain.

The possible formidable complications associated with the use of cautery at laparoscopy should be a caveat to the overzealous laparoscopic surgeon. To know when not to operate through the laparoscope is of paramount importance. The categories of mild and moderate endometriosis are useful anatomic guidelines to be used in making a decision. It is essential that, before one attempts to treat endometriosis at laparoscopy, one should be familiar with pelvic anatomy, take meticulous

care in assessing the extent and location of the disease, acquire a thorough training in laparoscopic surgery, and have experience in the use of cautery during pelvic surgery.

In summary, laparoscopic treatment of mild or moderate endometriosis in infertile women appears to be a safe, effective operative procedure which can be accomplished on an outpatient basis, and which may be performed under local anesthesia in certain patients. The number of pregnancies associated with this treatment is comparable to that with most other current forms of therapy. Since 50% of the pregnancies that will occur may be expected within 4 to 5 months, and 88% within 12 months, a patient who is not pregnant within 1 year of treatment may need to be reevaluated.

#### REFERENCES

- 1. Kistner, R. W.: Endometriosis and infertility. Clin. Obstet. Gynecol. 22:101, 1979.
- Acosta, A. A., Buttram, V. C., Besch, P. K., Malinak, L. R., Franklin, R. R., and Vanderheyden, J. D.: A proposed classification of pelvic endometriosis, Obstet. Gynecol. 42:19, 1973.
- 3. Hasson, H. M.: Electrocoagulation of pelvic endometriotic lesions with laparoscopic control, Am. J. Obstet. Gynecol. 135:115, 1979.
- Eward, R. D.: Cauterization of stages I and II endometriosis and the resulting pregnancy rate, in Phillips, J. M., editor: Endoscopy in Gynecology, Downey, California, 1978, American Association of Gynecologic Laparoscopists, p. 276.
- 5. Buttram, V. C.: Conservative surgery for endometriosis in the infertile female: A study of 206 patients, with implications for both medical and surgical therapy, Fertil. Steril. 31:117, 1979.
- Katayama, K. P., Manuel, M., Jones, H. W., and Jones, G. S.: Methyltestosterone treatment of infertility associated with pelvic endometriosis, Fertil. Steril. 27:83, 1976.
- 7. Garcia, C. R., and David, S. S.: Pelvic endometriosis: Infertility and pelvic pain, Am. J. Obstet. Gynecol. 129:740, 1977.
- 8. Decker, W. H., and Lopez, H.: Conservative surgical treatment of endometriosis and infertility, Infertility 2: 155, 1979.

- 9. Sadigh, H., Naples, J. D., and Batt, R. E.: Conservative surgery for endometriosis in the infertile couple, Obstet. Gynecol. 49:562, 1977.
- Hammond, M. G., Hammond, C. B., and Parker, R. T.: Conservative treatment of endometriosis externa: The effects of methyltestosterone therapy, Fertil. Steril. 29:651, 1978.
- Dmowski, W. P., and Cohen, M. R.: Antigonadotropin (Danazol) in the treatment of endometriosis, Am. J. OBSTET. GYNECOL. 130:41, 1978.
- Moghissi, K. S., and Boyce, C. R.: Management of endometriosis with oral medroxyprogesterone acetate, Obstet. Gynecol. 47:265, 1976.
- 13. Hammond, C. B., Rock, J. A., and Parker, R. T.: Conservative treatment of endometriosis: The effects of limited surgery and hormonal pseudopregnancy, Fertil. Steril. 27:756, 1976.
- Lundström, V., and Gréen, K.: Endogenous levels of prostaglandin F<sub>2α</sub> and its main metabolites in plasma and endometrium of normal and dysmenorrheic women, Am. J. Obstet. Gynecol. 130:640, 1978.
- Chan, W. Y., Dawood, M. Y., and Fuchs, F.: Relief of dysmenorrhea with the prostaglandin synthetase inhibitor ibuprofen: Effect on prostaglandin levels in menstrual fluid, Am. J. Obstet. Gynecol. 135:102, 1979.
- 15. Cheng, Y. S.: Ureteral injury resulting from laparoscopic fulguration of endometriotic implant, Am. J. Obstet. Gynecol. 126:1045, 1976.

#### XY gonadal dysgenesis in three siblings

S. A. PHANSEY, M.D.

R. SATTERFIELD, M.D.

R. J. JORGENSON, D.D.S.

C. F. SALINAS, D.D.S.

F. E. YODER, M.S.

R. S. MATHUR, Ph.D.

H. O. WILLIAMSON, M.D.

Charleston, South Carolina

Three tall, phenotypic female siblings with XY gonadal dysgenesis were found to have short fourth metacarpal bones (bilateral in two and unilateral in the other). Clitoromegaly was observed in the two older siblings, without hirsutism. Bilateral streak gonads were found in all three. A gonadoblastoma was present in the left streak gonad of the youngest, and an adenomatoid tumor in the left streak gonad of the oldest, who was diabetic. Determination of androgens from peripheral and gonadal venous plasma revealed androgen secretion by the streak gonads. On the basis of clinical findings, familial tendency, and androgen secretion from the streak gonads in these patients, it is proposed that the XY gonadal dysgenesis represents a severe form of male pseudohermaphroditism. (AM. J. OBSTET. GYNECOL. 138:133, 1980.)

THIS REPORT describes three sisters with XY gonadal dysgenesis. The youngest had a small gonadoblastoma, and the oldest had an adenomatoid tumor, each in the left streak gonad.

#### Case reports

Case 1 (D. M.) (Fig. 1). This 20-year-old woman was referred for evaluation of primary amenorrhea, absence of secondary sex characteristics, and hypergonadotropism. She was a tall, phenotypic woman with minimally developed breasts, which was attributed to use of oral contraceptives for 2 months prior to referral. Physical abnormalities noted were sparse axillary and pubic hair, presence of short fourth metacarpal bones bilaterally, and slightly enlarged clitoris (Table I). She had a small normal vagina, hypoplastic cervix, and uterus with no adnexa palpable. An intravenous pyelogram, electrocardiogram, and glucose tolerance test were normal. Ophthalmologic examination was nor-

From the Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, and Department of Cytogenetics, Medical University of South Carolina.

Supported by Grant RR 1070 from the General Clinical Research Center, Medical University of South Carolina.

Received for publication March 25, 1980.

Accepted April 16, 1980.

Reprint requests: S. A. Phansey, M.D., Medical University of South Carolina, 171 Ashley Ave., Charleston, South Carolina 29403.

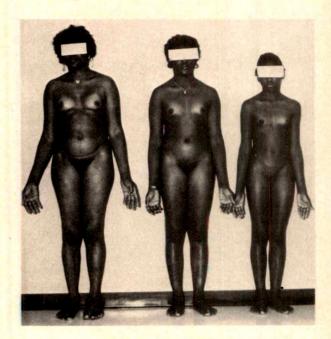


Fig. 1. Three siblings with XY gonadal dysgenesis.

mal for color vision and visual acuity. An audiogram showed mild neural loss of hearing bilaterally. Bone x-ray examination revealed unfused epiphyses of the elbows, wrists, interphalangeal, and knee joints. Laparotomy disclosed a small normal uterus, fallopian tubes, and bilateral streak gonads. Hysterectomy, bilat-

Table I. Clinical and histologic findings in three siblings

	Case 1	Case 2	Case 3
Presenting symptoms	Amenorrhea, lack of secondary sex characteristics	Same as in Case 1	Same as in Case 1
Medical history	None	Diabetes mellitus	None
Marital status	Single	Married	
Age (yr)	20	33	Single
Blood pressure (mm Hg)	118/76	122/80	13
Weight (kg)	58	77.5	100/70
Height (cm)	172.5	174	38.7
Span (cm)	178	178	147
Lower segment (cm)	90	91	155
Sitting height (cm)	77.5	86.5	80
Carrying angle (degrees)	11	16	76
Hair			16
Han	Sparse pubic and axillary	Sparse pubic and axillary	Very sparse pubic and axillary hair, no hirsutism
Nevi	None	None	
Facial features	Normal	Coarse	Single nevus on upper lip
Breasts	Minimally developed	Minimally developed	Slight facial asymmetry
Clitoris	Prominent	Prominent	None
Extremities	Short fourth metacarpal bones		Normal
	bilaterally	Short left fourth metacarpal bone	Short fourth metacarpal bones bilaterally
Gonads	Bilateral streaks	Bilateral streaks with adenoma- toid tumor in left gonad	Bilateral streaks with gonado- blastoma in left gonad

Table II. Sex steroid data at the time of operation, expressed in nanograms per 100 ml of venous plasma

Patient	Progesterone	17-Hydroxy- progesterone	Dehydroepi- androsterone (DHA)	Dehydroepi- androsterone sulfate (DHAS*)	Androstenedione	Estradiol	Testosterone
D. M.							
Peripheral	153	212	227	385	33	BLS†	0.4
Gonadal	158	283	256	345	153		34
M. M.‡		-00	200	343	133	BLS	153
Peripheral	43	BLS	46	39	11	DIC	
Gonadal	38	BLS	64	32	7.7	BLS	45
E. M.		DES	0.1	32	16	BLS	85
Peripheral	41	38	248	150	49	DIC	10.5
Gonadal	119	68	440		42	BLS	16.5
- Commun	113	00	440	120	201	BLS	41.8

<sup>\*</sup>Expressed in micrograms per 100 ml.

eral gonadectomy, and appendectomy were performed. The gonadal streaks consisted of fibrous tissue similar in arrangement to normal ovarian stroma but lacking germ cells or follicular structures. Leydig cells and remnants of rete ovarii were present. Tubular structures identical to epididymal tubules were also seen in the left adnexa.

Case 2 (M. M.) (Fig. 1). This 33-year-old phenotypic woman was previously diagnosed elsewhere as being XY gonadal dysgenetic with diabetes mellitus. She was placed on 60 units of NPH insulin and sequential Premarin and Provera therapy.

Physical examination revealed a tall individual with coarse facial features, and large hands and feet (size 10 shoes). The breasts were minimally developed, with pigmented areolae and erect nipples, probably due to previous hormonal therapy. Axillary and pubic hair

was sparse. Pelvic examination disclosed a prominent clitoris, but otherwise normal external genitalia, small normal vagina, cervix, and uterus without palpable adnexa. The only other abnormality observed was a short left fourth metacarpal bone. Findings by cardiogram, audiogram, intravenous pyelogram, and ophthalmologic examination were normal. Bone x-ray examination showed unfused epiphyses of iliac crests, slight thoracic scoliosis, overgrowth of the medial condyle of the femurs, and a short left fourth metacarpal bone.

Exploratory laparotomy was performed, with bilateral gonadosalpingectomy. Gross examination of the left gonad revealed a 3-mm tumor in the medial pole. Histologic examination of both gonads revealed ovarian stroma without ova or follicles. Remnants of rete ovarii and scattered nests of Leydig cells were present.

<sup>†</sup>Below limits of sensitivity (5 nanograms per 100 ml)

<sup>‡</sup>M. M. had been on estrogen treatment until 3 days prior to collection of the samples of blood.

XY gonadal dysgenesis 135

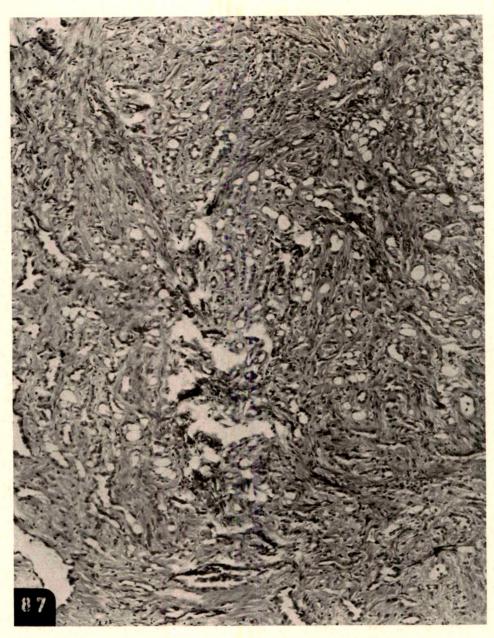


Fig. 2. Adenomatoid tumor in left gonadal streak of the oldest sibling (M. M.)

The grossly recognizable lesion in the left gonad was an adenomatoid tumor (Fig. 2). Mesonephric remnants were also present.

Case 3 (E. M.) (Fig. 1). This 13-year-old girl, youngest of the siblings, was seen with absence of menarche and secondary sexual characteristics. She had a slight facial asymmetry. A single nevus was present over the upper lip. Breast tissue was absent, with flat nipples and hypopigmented areolae. She had very sparse axillary and pubic hair. Pelvic findings included normal female external genitalia, hypoplastic vagina, cervix, and uterus with impalpable adnexa. Other abnormal findings revealed short fourth metacarpal

bones bilaterally, unfused epiphyses of iliac crests, and overgrowth of both medial femoral condyles. The electrocardiogram and ophthalmological examination, including color vision, were normal.

Surgical exploration was performed, with bilateral gonadectomy. Histopathologic findings were consistent with streak gonads with ovarian type of stroma that contained blood vessels, fibrocollangenous tissue, smooth muscle, and small tubular structures of cuboidal and low columnar cells consistent with rete ovarii or mesonephric remnants. Clusters of Leydig cells were present. The left gonad contained an area, 1 by 1.4 cm in size, of classic calcified gonadoblastoma with small

136 Phansey et al.



Fig. 3. Gonadoblastoma with degenerating germ cells and Leydig cells. A typical gonadoblastoma in left gonadal streak of the youngest sibling (E. M.)

delineated nests of germ and Sertoli cells surrounded by compressed capsular tissue (Fig. 3).

#### Biochemical and endocrine studies

Laboratory investigations for the three siblings included normal thyroid functions with no detectable antibodies and normal serum cortisol levels. Liver enzymes were normal, except for slightly elevated alkaline phosphatase. Gonadotropins were in the castrate range. Samples of blood from peripheral as well as gonadal veins were analyzed for progesterone, 17-hydroxyprogesterone, dehydroepiandrosterone, dehydroepiandrosterone sulfate, estradiol, androstenedione, and testosterone, as described previously, and the findings are shown in Table II.

Buccal and vaginal smears were X, chromatinnegative. Chromosomal analysis on peripheral leukocyte culture and skin fibroblasts, performed by counting 35 cells in each tissue, showed 46,XY karyotype with no detectable mosaicism in the three siblings.

#### Family history

The only significant finding in regard to the family was the incidence of diabetes. Two paternal uncles were severely diabetic, one of whom had died of the disease. The mother is 50 years old and is mildly diabetic. The 62-year-old father is tall and phenotypically normal. There was no instance of thyroid disease in the family. All siblings, including the affected members, were born normally, with no history of prematurity. There is no history of consanguinity, to the best of our knowledge. Xga blood group studies were performed for all siblings and the parents (Fig. 4). Two of the affected siblings, two normal siblings, and the mother were Xga positive.

#### Comment

Swyer<sup>2</sup> first described as a new form of male pseudohermaphroditism a tall, phenotypic female with primary amenorrhea, undeveloped secondary sex characteristics, and X, chromatin-negative pattern. Hoffenberg and Jackson<sup>3</sup> reported similar cases in 1957, describing them as variants of gonadal dysgenesis. They introduced the term pure gonadal dysgenesis for patients who have dysgenetic gonads without the external physical stigmas of Turner's syndrome. Harnden and Stewart<sup>4</sup> were the first to report an XY karyotype in a patient with pure gonadal dysgenesis. Since then, the spectrum of pure gonadal dysgenesis has come to include phenotypically female patients with dysgenetic gonads without Turner's features, irrespective of their chromosomal pattern. To the best of our knowledge, the present report is the first to describe three XY gonadal dysgenetic members in the same generation of one family. Although the available data are not sufficient to establish the mode of inheritance in this family, characteristic distribution of affected individuals in other family reports suggests X-linked recessive inheritance.5-7

The absence of testes in individuals with apparently normal 46,XY karyotype has been an enigma. Recently, it has been postulated that a serologically detectable plasma-membrane protein, H-Y antigen, is necessary to induce normal testicular organization.8, 9 It is assumed that XY individuals who do not possess the H-Y antigen (H-Y-) would fail to develop testes. Conversely, if H-Y antigen is expressed in the absence of a Y chromosome, normal testicular formation could occur, producing 45,X or 46,XX males. On the basis of experimental data, it appears that dissemination of H-Y antigen in the primitive gonad and the binding of it to the specific gonadal surface receptors are critical for inducing normal testicular organization.10 Func-

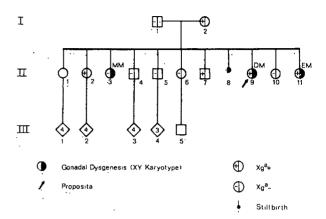


Fig. 4. Pedigree of the family with results of Xg blood grouping. II 3, II 9, and II 11 are the patients presented in this report.

tional absence of H-Y antigen due to a lack of release of it or inability of the antigen to bind to specific cell receptors could result in the failure of testes to form. This may explain the absence of testes in certain XY gonadal dysgenetic patients despite the presence of H-Y antigen (H-Y+). Loss of H-Y antigen could also occur if a portion of the Y chromosome is deleted or translocated. This loss may create an apparent absence of H-Y antigen, with the residue being below the critical level required to induce testicular differentiation. In patients with familial XY gonadal dysgenesis who have an X-linked recessive mode of inheritance, the absence of testes is possibly due to a mutational suppression of H-Y antigen activity by regulatory elements of the X chromosome.11 Available data suggest that development of the mammalian testes requires a normal function of the X chromosome.12

Xga blood group studies were performed with the hope that the Xga positive or negative groups would establish X-linkage and might decide the manner of inheritance of this disorder. Although the data obtained are insufficient to produce any conclusions about linkage, the family pattern shows at least one recombination between the locus responsible for the disorder and the Xga locus. This suggests that the two loci are not closely linked.

Primary adenomatoid tumor has not been reported previously in a gonadal streak. It is commonly found in male gonads but is a rare finding in the ovaries. 13, 14 This fact and the well-established malignant potential of dysgenetic gonads in 46,XY individuals<sup>15</sup> seem to suggest that in these individuals an abnormality of the genetic control of gonadal differentiation results in testicular dysgenesis or gonadal streaks.

#### REFERENCES

- Mathur, S. R., Sagel, J., Williamson, H. O., Colwell, J. A., and Nair, R. M. G.: Evaluation of the pituitary gonadal axis using gonadotropin releasing hormone and its superactive analogue, in Gupta, D., and Voeltaire, F., editors: Hypothalamic Hormones, Chemistry, Physiology and Clinical Application, Weinheim, 1978, Verlag Chemie, p. 509.
- Swyer, G. I. M.: Male pseudohermaphroditism: A hitherto undescribed form, Br. Med. J. 2:709, 1955.
- Hoffenberg, R., and Jackson, W. P. U.: Gonadal dysgenesis in normal looking females, Br. Med. J. 1:1281, 1957.
- 4. Harnden, D. G., and Stewart, J. S. S.: The chromosomes in a case of pure gonadal dysgenesis, Br. Med. J. 2:1285, 1959
- German, J., Simpson, J. L., and Chaganti, R. S. K.: Genetically determined sex-reversal in 46,XY humans, Science 202:53, 1978.
- Chemke, J., Carmichael, R., Stewart, J. M., Geer, R. H., and Robinson, A.: Familial XY gonadal dysgenesis, J. Med. Genet. 7:105, 1970.

- Sternberg, W. H., Barclay, D. L., and Kloepfer, H. W.: Familial XY gonadal dysgenesis, N. Engl. J. Med. 278: 695, 1968.
- 3. Silvers, W. K., and Wachtel, S. S.: HY antigen: Behavior and function, Science 195:956, 1977.
- Ohno, S.: The role of HY antigen in primary sex determination, J.A.M.A. 239:217, 1978.
- 13. Wachtel, S. S.: The genetics of intersexuality: Clinical and theoretic perspectives, Obstet. Gynecol. 54:671, 1979.
- McFeely, R. A., Hare, W. C. D., and Biggers, J. D.: Chromosome studies in 14 cases of intersex in domestic mammals, Cytogenetics 6:242, 1967.
- 12. Bernstein, R., Koo, G. C., and Wachtel, S. S.: Abnormality of the X chromosome in human 46,XY female siblings with dysgenetic ovaries, Science 207:768, 1980.
- 13. Jackson, J. R.: The histogenesis of the adenomatoid tumor of the genital tract, Cancer 11:337, 1958.
- Williamson, H. O., and Moore, M. P.: Ovarian and parovarian adenomatoid tumors, Am. J. Obstet. Gynecol. 90:388, 1964.
- Schellhas, H. F.: Malignant potential of the dysgenetic gonad. Part I, Obstet. Gynecol. 44:298, 1974.

#### The role of adjuvant therapy in Stage I ovarian cancer

MYROSLAW M. HRESHCHYSHYN, M.D.<sup>1</sup>
ROBERT C. PARK, M.D., COLONEL, M.C., USA<sup>2</sup>
JOHN A. BLESSING, Ph.D.<sup>3</sup>
HENRY J. NORRIS, M.D.<sup>4</sup>
DAVID LEVY, M.D.<sup>5</sup>
LEO D. LAGASSE, M.D.<sup>6</sup>
WILLIAM T. CREASMAN, M.D.<sup>7</sup>
Philadelphia, Pennsylvania

Women with Stage I epithelial carcinoma of the ovary were initially treated by an extirpative operation and were subsequently randomized to either no further treatment, radiotherapy, or chemotherapy. Only two patients (6%) treated with chemotherapy developed recurrence, compared to five (17%) and seven (30%) patients in the no-treatment and radiotherapy regimens, respectively (P < 0.05). All patients, with the possible exception of those with Stage IA(1)g1, appeared to benefit from adjuvant chemotherapy compared to no treatment or radiotherapy. (AM. J. OBSTET. GYNECOL. 138:139, 1980.)

CANCER of the ovary is the second most common gynecologic malignancy, with 17,000 new cases yearly in this country. Eleven thousand women die of this disease annually, which makes it the most lethal gynecologic tumor. Most ovarian malignancies are epithelial

From the Gynecologic Oncology Group.

Grant support information is given at the end of the article.

Received for publication August 6, 1979.

Revised March 17, 1980.

Accepted March 27, 1980.

Reprint requests: Myroslaw M. Hreshchyshyn, M.D., Gynecologic Oncology Group Headquariers, Suite 430, 1234 Market St., Philadelphia, Pennsylvania 19107.

<sup>1</sup>Division of Gynecologic Oncology, Department of Gynecology and Obstetrics, State University of New York at Buffalo, Buffalo, New York; 2Gynecology Oncology Service, Walter Reed Army Medical Center, and Department of Obstetrics and Gynecology, Uniformed Services, School of the Health Sciences, Washington, D.C.; Gynecologic Oncology Group, Reswell Park Memorial Institute, Buffalo, New York; Department of Gynecology and Breast Pathology, Armed Forces Institute of Pathology, Washington, D. C.; Department of Radiation Oncology, University of Alabama, Birminghan, Alabama; Division of Gynecologic Oncology, Departmen. of Obstetrics and Gynecology, University of California at Los Angeles Center for the Health Sciences, Los Angeles, Califorinia, (supported by United State: Public Health Service Grant CRC RR 865); Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Dure University Medical Center, Durham, North Carolina.

in origin, and more than 60% are in Stages III and IV at the time of diagnosis.<sup>2</sup> Late detection is the rule because symptoms of early ovarian cancer are nonspecific, so that a diagnosis may be difficult to make and may be infrequently made. Even when the disease is early and confined to the ovaries, 5-year cure rates are usually only 60%.<sup>3-6</sup>

The initial management of patients with resectable ovarian cancer is clearly surgical. The value of pelvic irradiation and chemotherapy postoperatively is not clear, since there has been no randomization or consistency in their use.7-11 In a small number of patients with Stage I cancer of the ovary, there was no appreciable difference in survival when chemotherapy was used in a random fashion. 12 In an uncontrolled study, Hanks and Bagshaw<sup>13</sup> reported a 5-year survival rate of 82% in 21 patients with completely resected ovarian neoplasms who were treated postoperatively with pelvic radiation up to 5,500 rads. Similar results were reported by Delclos and Quinlan14 in 21 patients with Stage I neoplasms, who also were treated postoperatively with radiotherapy, but Perez and Bradfield15 reported only 60% survival in a similar group of patients treated in like manner. Munnell<sup>16</sup> detected an improvement in reports of 5-year survival rates during the period from 1952 to 1961, over those in the years 1922 to 1961, which he attributed to the more frequent use of postoperative radiotherapy as well as more aggressive and extensive operative procedures. The im-

**Table I.** Distribution of tumors by cell type and grade

		Grade	
Cell type	1	2	3
Clear-cell carcinoma	4	5.	0
Endometroid adenocarcinoma	15	7	5
Mucinous adenocarcinoma	19	3	0
Unclassified carcinoma	1	0	0
Undifferentiated carcinoma	0	0	6
Serous adenocarcinoma	14	3	4
Total	53	$\overline{18}$	$\overline{15}$

Table II. Grade by treatment

,	,	Grade	
Therapy	1	2	3
No therapy	17	7	5
Radiation therapy	14	5	4
Chemotherapy	22	6	6
Total	<u>22</u> 53	18	$\frac{-6}{15}$

Table III. Stage by treatment

Therapy	Stage					
	IA(1)	IA(2)	<i>IB</i> (1)	. IB(2)		
No therapy	18	11	0	. 0		
Radiation therapy	11	8	1	3		
Chemotherapy	<u> 19</u>	9	<u>3</u>	3		
Total	48	28	4	6		

provement attributed to radiation occurred in FIGO (International Federation of Gynaecology and Obstetrics) Stage II and Stage III cancer, whereas operative intervention alone in Stages IA and IB cancer produced better survival than when radiation was added.

Although some have reported benefit, the role of adjuvant chemotherapy in early ovarian cancer has not been established. In a small and uncontrolled series in which chlorambucil was used as an adjuvant to operation in patients with Stages I and IIA cancer, there were fewer recurrences than expected.<sup>17</sup> Thus, the value of adding various therapeutic measures to the surgical management of resectable ovarian carcinoma has not been determined.

The purpose of this study was to evaluate the role of adjuvant pelvic radiation and chemotherapy in patients with Stage I epithelial ovarian cancer in a randomized clinical trial.

#### Material and methods

Patients in whom Stage I epithelial ovarian carcinoma was determined by exploratory laparotomy were

eligible for this study. Routine exploration of the diaphragm, sampling of the lymph nodes, peritoneal cytologic examination, and omentectomy were not required, since the possible significance of them was not recognized when this study was activated in 1971. Within 8 weeks after total abdominal hysterectomy and bilateral salpingo-oophorectomy, eligible patients were randomly assigned to one of three treatment regimens: (1) no further treatment, (2) pelvic radiation, or (3) chemotherapy without regard to substage of cancer, type of tumor, or degree of histologic differentiation.

Excluded from the study were patients with epithe-lal tumors of low malignant potential and patients with escites; patients with second malignancies other than skin cancer; patients who had received radiotherapy or chemotherapy with cytotoxic agents; patients who had hematopoietic depression, septicemia, or severe infection, gastorintestinal bleeding or significant impairment of hepatic and renal function; and patients whose circumstances would not permit completion of the study or the required follow-up. Three patients who were initially treated with only bilateral salpingo-cophorectomy and who had no tumor on endometical circutage were allowed to remain in the study.

Patients who were assigned to the radiotherapy regimen received 5,000 rads to the pelvis in 5 to 6 weeks, with a daily dose of 160 to 200 rads five times a week from x-ray generators which produced a peak photon energy of one million electron volts or more or from cobalt-60 irradiators. The margins of the radiation portals were defined as follows: (1) superior—the upper margin of the sacroiliac joint; (2) inferior—the upper third of the obturator foramen; and (3) lateral—1 cm beyond the lateral margins of the bony pelvis at the widest plane of the pelvis.

Patients who were assigned to the chemotherapy regimen received melphalan, 0.2 mg per kilogram, daily orally for 5 days every 4 weeks for 18 months if the leukocyte count was at least 3,000 per cubic millimeter and the platelet count was at least 150,000 per cubic millimeter.

Patients were evaluated for recurrence of the tumor and treatment toxicity at least once a month while on therapy. This included determination of the hemoglobin level and the white blood cell and platelet counts. X-ray films of the chest and intravenous pyelograms were required at 6-month intervals for the first 2 years, and annually thereafter. Other evaluations and more frequent examinations were performed when needed.

The Radiologic Physics Center supervised radiation dosimetry for this trial. All materials on each patient, including beam verification, film, and isodose distribution curves, histologic slides, and study forms containing all pertinent data on patient eligibility, treatment, and adverse effects were reviewed by the appropriate committees of quality control, gynecologic management, radiotherapy, chemotherapy, and pathologic study. After review by two pathologists for eligibility, the histologic slides in all cases were reviewed again for final classification by one of the authors (H. J. N.).

The grading of the tumors was made on conventional lines, on the basis of the degree of gland formation (differentiation) and on cytologic criteria. The cytologic criteria included the uniformity of the cells and nuclei, the degree of nuclear hyperchromatism, the nuclear-cytoplasmic ratio, the number and size of nucleoli, and the frequency of mitotic figures per highpower field. The grade was assigned on the basis of the least differentiated areas within the tumor.

Duration of progression-free interval was calculated from the date of randomization and was compared by therapy by means of the Breslow test. Recurrence rates were compared by Fisher's exact test or its large-sample approximation.

#### Results

One hundred sixty-eight patients were entered into this protocol from June 25, 1971 to March 17, 1978. Of these, 86 were evaluable in that they were in the proper stage, had received the prescribed treatment, and had been adequately followed. Patients not included were ineligible (most were judged to have a tumor of low malignant potential), or were inevaluable (most patients in this category either refused the prescribed therapy, were removed by their physician, or had treatment violation), or had inadequate tissue for pathologic review. An equal number of patients were removed from the study in each of the three treatment categories.

Patients were randomized into three postoperative categories: no further therapy (29 evaluable patients), radiation therapy (23 evaluable patients), chemotherapy (34 evaluable patients). These patients were followed for 4 to 83 months, with a median follow-up period of 36 months.

Table I evaluates the histologic features of the tumors with regard to grade. The grade of the tumor correlated with the cell type. In what is considered to be "good" histologic cell types (clear cell, endometrioid, and mucinous), 65% were grade 1, as compared to 53% in the "poor" cell type. There was a larger percentage of these histologic cell types (clear cell, endometrioid, mucinous) in the no-treatment category (85%) than in the radiation-therapy (57%) and melphalan (62%) categories.

The grade of the tumor was similar in all three post-

Table IV. Stage by grade

		Grade	
Stage	1	2	3
IA(1)	34	10	4
IA(2)	16	5	7
IB(1)	0	2	2
IB(2)	_3	_1	2
Total	$\frac{3}{53}$	18	15

Table V. Comparison of therapy and recurrence

		Recur	тепсе
The rapy	No. of patients	No.	%
No therapy	29	5	17
Radiation therapy	23	7	30
Chemotherapy	34	2	6

Table VI. Site of recurrence by therapy

Site	No therapy	Radiation therapy	Chemotherapy
Pelvis Abdomen Pelvis and abdomen Distant	$   \begin{bmatrix}     1 & (3\%) \\     0 \\     3 \\     1   \end{bmatrix}   (14\%) $	$   \begin{bmatrix}     1 & (4\%) \\     2 \\     2 \\     2   \end{bmatrix}   (26\%) $	$\begin{bmatrix} 1 & (3\%) \\ 0 \\ 0 \\ 1 \end{bmatrix} (3\%)$

Table VII. Stage by therapy for failures

	Recurrences by stage						
	IA(	(1)	IA(	(2)	1	В	
Therapy	No.	%	No.	%	No.	%	
No therapy	2	11	3	27	_		
Radiation therapy	2	18	1	12	4	100	
Chemotherapy	1	5	1	11	0		

operative treatment regimens (Table II). The substage within Stage I and the type of treatment used are noted in Table III. There were no Stage IB lesions in the no-treatment category. Seventeen percent of the patients treated with radiation therapy had Stage IB lesions, as did 18% of the patients treated with chemotherapy. Of patients in the no-treatment category, 62% had a Stage IA(1) lesion, in comparison with 48% in the radiation group and 56% in the chemotherapy group. The grade of the tumor with regard to substage is shown in Table IV. As the substage increased, the grade of the tumor also increased. Only 8% of the stage IA(1) lesions were grade 3, compared to 33% of the Stage IB(2) lesions.

Of the 86 patients available for evaluation, 14 developed recurrences (Table V). Only 6% of the patients

**Table VIII.** Comparison of failures by cell type and grade

	Grade				
Cell type	1	2	3		
Clear cell Endometroid Mucinous Undifferentiated adeno- carcinoma Serous	$   \begin{bmatrix}     1 \\     0 \\     1   \end{bmatrix}     5\%   $ $   \begin{bmatrix}     0 \\     1   \end{bmatrix}     29\%   $	$ \begin{vmatrix} 0 \\ 2 \\ 1 \end{vmatrix} 20\% \\ 0 \\ 33\% $			

**Table IX.** Relationship of the grade of the tumor to its recurrence

		Recur	rence
Grade	No. of patients	No.	%
1	53	6	11
2	18	4	22
. 3	15	4	27

Table X. Comparison of recurrences by grade and treatment

Therapy	Grade							
	1		2		3			
	No.	%	No.	%	No.	%		
No therapy	1	6	2	28	2	40		
Radiation therapy	4	29	2	40	1	25		
Chemotherapy	1	4	0		1	17		

**Table XI.** Relationship of tumor stage and recurrences

		Recurrence		
Stage	No. of patients	No.	%	
IA(1)	48	5	10	
IA(2)	28	5	18	
IB(1)	4	1	25	
IB(2)	6	3	50	

Table XII. Comparison of recurrences by stage and treatment

	Recurrences by stage							
	IA(1)		IA(2)		<i>IB</i> (1)		IB(2)	
Therapy	No.	%	No.	%	No.	%	No.	%
No therapy Radiation therapy	2 2	11 18	3	27 12	_ 1	100	- 3	100
Chemotherapy	1	5	1	11	ó	100	ő	100

who were treated with melphalan developed a recurrence, compared with 17% of those who received no creatment and 30% of those who were treated with -adiation therapy (P < 0.05). When patients who were udged to be inevaluable because of treatment protocol violation were included in the analysis, the trend with regard to recurrence favoring the melphalan arm remained unchanged. Radiation did not prevent pelvic recurrence (Table VI), since recurrences in the pelvis were equal among all treatment modalities. When the site of recurrence was outside of the pelvis, only 3% of patients treated with melphalan developed recurrences, compared to 14% and 26% of those in the notreatment and radiation therapy regimens, respectively (P = 0.036). When recurrences were evaluated with regard to the substage of disease, again, melphalan appeared to be better than no-treatment or radiation therapy in each of the substage categories, with the exception of the Stage IA(2) category, in which there was no difference between chemotherapy and radiation therapy (Table VII). When recurrences were evaluated with regard to the grade and cell type of the tumor, only six (10%) of the 58 patients with the "good" histologic cell types developed a recurrence, compared to eight (29%) with undifferentiated, unclassified, or serous cystadenocarcinoma who developed recurrence (Table VIII).

Only 11% of the patients with a well-differentiated lesion developed recurrence, in comparison to 22% and 27% with grade 2 and grade 3 lesions, respectively (Table IX). Table X evaluates recurrence, the grade of the tumor, and treatment modality. Here again, patients treated with melphalan tended to do as well as, or better than, patients in the no-treatment category or those treated with radiation therapy, within the respective grades.

When recurrences were compared by substage, a definite trend was apparent. Only 10% of patients with Stage IA(1) lesions developed recurrences, compared to 50% of those with Stage IB(2) lesions (Table XI). When the substages were evaluated with regard to the treatment categories, melphalan was, in each substage, equal or superior to no treatment or radiation therapy (Table XII).

#### Comment

Since the start of this study it has become recognized that many prognostic factors are present in cases of ovarian cancer. These include whether the ovarian capsule is invaded by tumor, the presence of malignant cells in peritoneal washings, the stage of disease, the type and grade of tumor cell, the amount of tumor left

in situ after surgical procedures, and the type of postoperative therapy. Recently, a group from the Mayo Clinic defined the gross characteristics of Stage I disease with regard to whether the ovarian mass was ruptured, adherent, intracystic, or extracystic. They thought that these factors should be considered in the selection of proper treatment of the specific lesion, and that such individualized treatment should give an improved rate of survival.

Surgical intervention is the initial treatment in ovarian cancer, but, even in early disease, when no gross evidence of spread beyond the ovary is found, the survival rate is only 60% at 5 years.3-6 To improve this survival rate, adjunctive therapy has been applied. Radiation therapy in small groups of patients has increased the survival rate, but side effects may be considerable. More recently, chemotherapy has improved the survival rate over that with operative intervention alone. Since there are multiple prognostic factors which can influence survival, a randomized prospective study was done to evaluate regimens of no therapy, pelvic irradiation, and chemotherapy.

In patients treated with chemotherapy, only two (6%) developed recurrence during the time interval that was followed. This compares with five recurrences (17%) among those patients who had no subsequent therapy, and seven recurrences (30%) among those treated with radiation therapy. The difference in the rate of recurrence (P = 0.047) is more meaningful when known prognostic factors are evaluated. Those patients who received no treatment subsequent to operation had a disease of lower stage-62% had Stage IA(1) lesions, in comparison to 56% of those treatec with chemotherapy and only 48% of these treated with radiation therapy. Even within the category of Stage IA(1) lesions, the patients treated with chemotherapy had fewer recurrences than those who received either no treatment or radiation therapy, although the numbers are small. And when the histologic findings were considered, 83% of those who received no treatment had favorable cell types (clear cell, endometrioid, mucinous), compared to 62% of those who received chemotherapy and 57% of those who were treated with radiation therapy. Only 10% of the patients with favorable cell types developed recurrence. Yet, 17% of the no-treatment group in this category developed a recurrence, as did 15% treated with radiation therapy and none who were treated with melphalan.

The grade of tumor was distributed equally among the three treatment groups, with only 11% recurrence in grade 1 compared to 22% and 27% in grade 2 and grade 3, respectively. Of patients who had grade 1 lesions, 5% who received melphalan developed a recurrence, 6% when no treatment was given, and 29% when radiation therapy was used (P = 0.059). When grade 2 and 3 were combined, 8% of those treated with melphalan developed recurrence, in comparison to 33% who had no treatment and 33% when radiation therapy was used (P = 0.273). The benefits of chemotherapy are suggestive, although not statistically significant.

Ovarian cancer, even in the early stages, is not always confined to the ovaries and may have diffuse peritoneal spread. This becomes evident when one evaluates the sites of recurrence by the method of treatment. Pelvic recurrence was equal in all treatment arms; however, when disease outside of the pelvis was evaluated, the only treatment modality which was systemic-melphalan—controlled the disease. Only one (3%) of the patients who was treated with chemotherapy had recurrence outside of the pelvis, in comparison to 14% of those who had no treatment and 26% of those who had radiation therapy. The reason for a lower recurrence rate in the no-treatment arm compared to radiation therapy may be the larger number of patients with Stage IA(1) carcinoma and favorable histologic cell types in the no-treatment category.

Only 10 patients (12%) had a Stage IB lesion. None was treated by surgical procedures alone. Of significance is the finding that among patients with Stage IB cancer, all four who were treated with radiation therapy developed recurrence, whereas all six who were treated with chemotherapy remain free of disease. It may be that in Stage IB disease the microscopic disease as well as the gross disease on a capsule indicates likely intra-abdominal spread, and, therefore, disease outside of the radiation field. Cytologic examination of the peritoneum may be helpful in detecting peritoneal spread; however, that procedure was not performed in many patients. In the small number of patients who had involvement of both ovaries, chemotherapy appeared to be superior to radiation therapy.

Even among patients with Stage IA(1) lesions, those who were treated with melphalan had fewer recurrences (5%) than did those who received either no treatment (11%) or radiation therapy (18%). When grade 1 disease was evaluated, there was no difference in the recurrence rates of patients treated with chemotherapy and those who received no treatment, but both groups did better than those treated with radiation therapy. Among patients with Stage IA(1)g1 lesions, only two had recurrences. One could question whether adjunctive therapy is needed in this very select group of patients. However, in other Stage IA substages and

grades, the recurrence rate varied from 12% to 33%, and, therefore, adjuvant chemotherapy appeared to be efficacious, since only 6% of the group treated with melphalan developed a recurrence.

Factors such as adherence of the tumor to the pelvic or abdominal viscera and tumor size of more than 10 cm appeared to carry a less favorable prognosis, but no statistically significant differences could be established, even when other factors, such as substage, grade, and treatment modality, were taken into consideration.

Important operative findings, such as involvement of the diaphragm, positive peritoneal cytologic findings, occult omental metastasis, and metastasis to lymph nodes, were not uniformly evaluated, since the significance of them was not generally appreciated when this study was initiated in 1971. These factors are currently taken into consideration before inclusion in present protocols. Occult disease outside of the pelvis is not rate in Stage I disease. One of the patients in the melphalan-treated group who had a "recurrence" was found to have a metastasis to the liver at the time of cholecystectomy only 6 months after the pelvic operation. Was this patient's carcinoma a true Stage I at the time of diagnosis?

This study suggests that, with the exception of Stage IA(1)g1 lesions, adjunctive therapy (melphalan) is beneficial in Stage I carcinoma of the ovary. A diagnosis of Stage IA(1)g1 can be made only after a thorough evaluation of the diaphragm and peritoneal surfaces is performed, multiple sections of a partial omentectomy specimen are taken, and peritoneal cytologic findings are evaluated along with the pelvic and para-aortic lymph nodes.

There is concern about the development of leukemia in the long-term use of alkylating agents. <sup>18</sup> To date, none of those patients treated with melphalan has de-

veloped leukemia. Whether adjuvant therapy with, for example, intraperitoneal colloid phosphorus would be as effective as that with melphalan without the potential of inducing malignancy is unknown, but is currently being evaluated.

The following are the institutions participating in the study and their supporting National Cancer Institute grant numbers: Walter Reed Army Hospital (CA 19189), University of California at Los Angeles (CA 13630), Hahnemann Medical College/Jefferson Medical College (CA 12478), New York Medical College (CA 12483), State University of New York at Buffalo (CA 12476), Emory University School of Medicine (CA 08121), George Washington University Medical Center (CA 13446); Henry Ford Hospital (CA 13887), University of Alabama Medical Center (CA 12484), University of Rochester Medical Center (CA 12482), Bowman Gray School of Medicine of Wake Forest University (CA 21946), Wayne State University School of Medicine (CA 12477), Northwestern Memorial Hospital (CA 12109), University of Southern California at Los Angeles (CA 13641), Brown University School of Medicine and Affiliated Hospitals (Roger Williams General Hospital) (CA 12481), Rush-Presbyterian St. Luke's Medical Center (CA 12485), University of Mississippi Medical Center (CA 13633), \*University of Utah Medical Center (CA 19189) (funded in part by the Gynecologic Oncology Group grant [CA 19189), Mt. Sinai School of Medicine (CA 12479), University of Colorado Medical Center (CA 15975), Hospital of the University of Pennsylvania (15977), Gynecologic Oncology Group (CA 19189). State University of New York at Syracuse was an unfunded participant.

We acknowledge the assistance of the Gynecologic Oncology Group Statistical Office and Gynecologic Oncology Group Operations Office in the preparation of the manuscript.

#### REFERENCES

- 1. Seidman, H., Silverberg, E., and Holleb, A. I.: Cancer statistics in 1976, Cancer 26:2, 1976.
- 2. Day, T. G., and Smith, J. P.: Diagnosis and staging of ovarian cancer, Semin. Oncol. 2:217, 1975.
- 3. Aure, J., Hoeg, K., and Kolstad, P.: Clinical and Histologic studies of ovarian carcinoma, Obstet. Gynecol. 37:1, 1971.
- 4. Fisher, R., and Young, R.: Advances in the staging and treatment of ovarian cancer, Cancer 39:967, 1977.
- Fuks, Z., and Bagshaw, M.: The rationale for curative radiotherapy for ovarian carcinoma, Int. J. Radiat. Oncol. Biol. Phys. 1:21, 1972.
- Webb, M. J., Decker, D. G., Mussey, E., et al.: Factors influencing survival in Stage I ovarian cancer, Am. J. OBSTET. GYNECOL. 116:222, 1973.
- 7. Kent, S. W., and McKay, D. G.: Primary cancer of the

- ovary and analysis of 349 cases, Am. J. Obstet. Gynecol. 80:430, 1960.
- 8. Kottmeier, H. L.: Ovarian cancer diagnosis and treatment, Med. Coll. Virginia Quart. 3:47, 1967.
- 9. Latour, J. P., and Davis, B. A.: A critical assessment of the value of x-ray therapy in primary ovarian cancer, Am. J. Obster. Gynecol. 74:968, 1957.
- Rubin, P., Grise, J. W., and Terry, R.: Has postoperative irradiation proved itself? Am. J. Roentgenol. Radium Ther. Nucl. Med. 88:849, 1962.
- Taylor, E. S., and Fox, F. J., Jr.: Is surgery alone adequate? Am. J. Roentgenol. Radium Ther. Nucl. Med. 88:846, 1962.
- 12. Smith, J. P., Rutledge, F. N., and Delclos, L.: Results of chemotherapy as an adjunct to surgery in patients with localized ovarian cancer, Semin. Oncol. 2:277, 1975.

- 13. Hanks, G. E., and Bagshaw, M. A.: Megavoltage radiation therapy and lymphangiography in ovarian cancer, Radiology 93:649, 1969.
- 14. Delclos, L., and Quinlan, B. J.: Malignant tumors of the ovary managed with postoperative megavoltage irradiation, Radiology 93:659, 1969.
- 15. Perez, C. A., and Bradfield, J. S.: Radiation therapy in the treatment of carcinoma of the ovary, Cancer 29:1027,
- 16. Munnell, E. W.: The changing prognosis and treatment in cancer of the ovary, Am. J. OBSTET. GYNECOL. 100:790,
- 17. Julian, C. G., and Woodruff, J. D.: The role of chemotherapy in the treatment of primary ovarian malignancy, Obstet. Gynecol. Surv. 24:1307, 1969.
- 18. Reimer, R. R., Hoover, R., Fraumeni, J. F., et al.: Acute leukemia after alkylating-agent therapy of ovarian cancer, N. Engl. J. Med. 297:177, 1977.

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following written statement, signed by one author: "The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C. V. Mosby Company in the event the work is published. The undersigned author warrants that the article is original, is not under consideration by another journal, and has not been previously published. I sign for and accept responsibility for releasing this material on behalf of any and all co-authors." Authors will be consulted, when possible, regarding republication of their material.

## Progressive histobiologic alterations in the development of vulvar cancer

Report of five cases

JOSEPH BUSCEMA, B.A.
J. DONALD WOODRUFF, M.D.

Baltimore, Maryland

Identification of the patient at risk for the development of cancer and the precursory histopathologic changes has led to improvement in 5-year survivals among patients with cancer of the cervix and endometrium. In contrast, there has been controversy as to these factors in discussions of vulvar neoplasia. This report of five cases of patients who developed invasive cancer after treatment for in situ disease attempts to define some of the at-risk factors, including the specific area at which three of the five malignancies subsequently developed. (AM. J. OBSTET. GYNECOL. 138:146, 1980.)

IDENTIFICATION of the patient at risk for the development of cancer and the precursory histopathologic patterns has been a persistent challenge for the oncologist. It is well known that the recognition of this patient and the critical tissue alterations has assisted in reducing the mortality of cervical and endometrial neoplasias. Nevertheless, current reviews have suggested that the previously well-accepted epithelial changes associated with vulvar cancer are not necessarily the critical precursory changes.1 Leukoplakia, a previously well-known premalignant condition, must be eliminated as a specific histopathologic entity since the term has been used to describe every known white lesion from vitiligo to invasive cancer.2 Furthermore, recent studies have suggested that the dystrophies, both hyperplastic and lichen sclerotic, rarely, if ever, progress to true invasive neoplasia.3 Consequently, the patient at risk for the development of vulvar neoplasia is not identified accurately at present, and the important histopathologic changes which may eventuate in invasive cancer are ill defined.

A recent review of 102 histopathologically acceptable cases of vulvar carcinoma in situ revealed that, al-

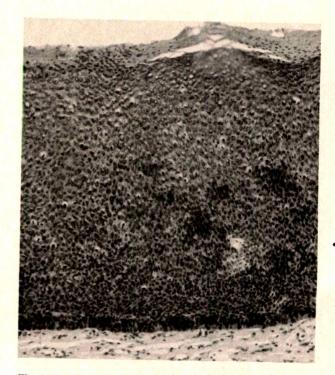
From the Department of Obstetrics and Gynecology, The Johns Hopkins Hospital.

Received for publication January 11, 1980.

Revised March 5, 1980.

Accepted March 27, 1980.

Reprint requests: J. Donald Woodruff, M.D., Department of Gynecology and Obstetrics, The Johns Hopkins Hospital, Baltimore, Maryland 21205.



**Fig. 1.** Case 1. In situ changes in anogenital area after hyster-ectomy for carcinoma in situ 2 years previously. (Original magnification, ×170.)

though local recurrences were frequent, the progression to invasive cancer was a rare occurrence. Furthermore, two of the four patients who subsequently developed invasive disease were 75 and 82 years of age at the time of the initial "in situ" diagnosis. In both cases, however, local recurrence with subsequent widespread invasive disease led to death within 24 months.



Fig. 2. Case 1. Biopsy tissue from anal orifice, 11 years after hysterectomy for cervical in situ cancer. (Original magnification, ×55.)

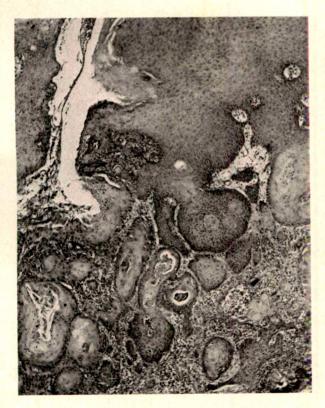


Fig. 3. Case 2. Invasive perianal squamous-cell cancer discovered 14 months after original biopsy of vulva revealed carcinoma in situ. (Original magnification, ×155.)

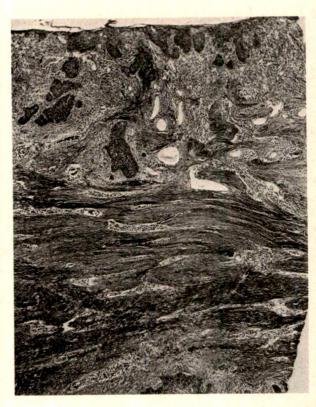


Fig. 4. Case 3. Invasive carcinoma at anal orifice. Lesion developed 11 years after treatment of original vulvar in situ neoplasia. (Original magnification, ×35.)

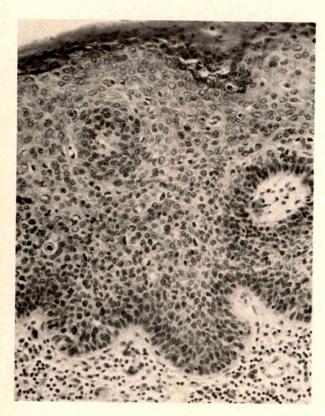


Fig. 5. Case 4. In situ vulvar neoplasia removed by wide local excision (in 1972). (Original magnification, ×225.)

The other 2 patients were 36 and 47 years of age at the time that invasive cancer was diagnosed, and in both instances the latter lesion developed at the anal orifice. Subsequent to this report of 102 cases of vulvar carcinoma in situ, a third patient, with a 10-year history of recurrent intraepithelial disease, had been treated for invasive cancer, again at the anal orifice.

The histopathologic features of the precursory in situ lesion, the critical perianal area, the immunologic competence,<sup>5</sup> and/or the age of the patient at risk are the important features of this review based on the above-mentioned five cases.

### Case reports

Case 1. A. H., a 37-year-old black woman, had a history of pulmonary sarcoidosis, first diagnosed in 1960. She had been treated with systemic corticosteroids since that date.

In 1962, the patient was treated by total abdominal hysterectomy for cervical carcinoma in situ. Within a year, a lesion was noticed on the vulva, and the lower third of the skin at the introitus was removed bilaterally. Approximately 6 to 9 months later, the patient was referred to The Johns Hopkins Hospital, where investigation revealed multifocal in situ neoplasia of the vulva, vagina, and perianal regions. In January, 1964, the patient was treated surgically by simple vulvectomy,

total vaginectomy with primary McIndoe procedure, and excision of perianal skin. Pathologic sections confirmed multifocal in situ disease in all areas (Fig. 1). Three years later, in 1967, the patient underwent an excisional biopsy of a perianal lesion, and review of the tissue revealed the presence of carcinoma in situ. The patient was treated by local irradiation (details are unknown). She was asymptomatic until October, 1973, at which time a "prolapse of tissue at the anal orifice" (Fig. 2) was biopsied, and the sections revealed invasive, cloacogenic carcinoma. The patient subsequently had a wide local excision of the perirectal tissues and adjacent rectal mucosa. The original diagnosis was confirmed (Fig. 2). Steroid therapy, which had been given for the previous 16 years, was thought to be unnecessary at this time and was discontinued. No adjunctive therapy was given. As of March, 1977 (3 years after the last surgical procedure), the patient had no recurrence.

In this case the patient was immunosuppressed, and possibly this factor was important in the genesis of the numerous local recurrences and eventually invasive cancer. Finally, the role of radiation therapy as a carcinogenic stimulus is unknown, but may also have been a significant factor in converting the local in situ neoplasm into invasive cancer, a sequence of events recognized in "verrucous carcinomas."

Case 2. P. F., a 36-year-old white woman, first presented in April, 1973, with a gross vulvar lesion. Excisional biopsy revealed the presence of carcinoma in situ. The patient was treated with topical 5-fluorouracil (Efudex 5%). Approximately 1 year later, a vaginal hysterectomy was performed for uterine prolapse and stress urinary incontinence. Approximately 1 month postoperatively, the patient was found to have a painful thrombosed hemorrhoid. The latter was incised and a biopsy was performed. The pathologic study revealed invasive squamous-cell carcinoma in the excised tissues (Fig. 3) which had undoubtedly been present at the time the original vulvar lesion was diagnosed. An abdominoperineal procedure was performed. Although the patient was lost to follow-up 14 months later, there had been no evidence of recurrence at the operative site or on the vulva.

It is noteworthy that there was no apparent systemic disease which may have contributed to the development of the invasive cancer. The patient was known to have asthma, but specific medication, such as steroid therapy, was not documented.

Case 3. E. S., a white woman, was first seen in 1969, at the age of 32 years, complaining of vulvar irritation. Biopsy revealed carcinoma in situ. The patient was treated by a "total vulvectomy." Histopathologically documented recurrence in the perianal tissue 1 year later was treated by excision, but additional therapy was not instituted at that time. In 1976, vulvar biopsies confirmed recurrence of in situ neoplasia, and treatment with topical 5-fluorouracil was instituted. Approximately 4 months later, repeat biopsies revealed persistence of the in situ disease, and in August, 1977,

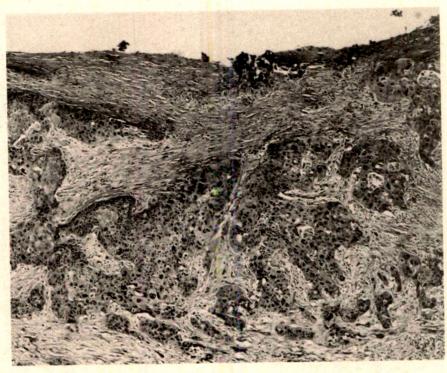


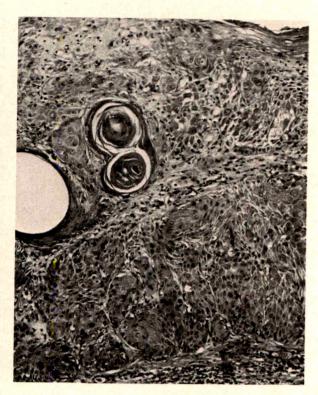
Fig. 6. Case 4. Invasive squamous-cell carcinoma developed in external genital area 3 years after the excision of in situ lesion seen in Fig. 5. (Original magnification ×65.)

the patient underwent a Whitehead procedure with excision of recurrent disease at the fourchette and in the perianal area. In March, 1979, 20 months later, biopsy of the perianal tissue revealed moderately well-differentiated invasive squamous-cell carcinoma (Fig. 4). Wide local excision of the lesion with part of the involved anal sphincter was carried out. Pathologic study confirmed the presence of infiltrating squamous-cell carcinoma in the fibromuscular tissue between 7 and 11 o'clock. The patient has recovered well and is being followed carefully. She is considered to be a candidate for immunotherapy.

In summary, this patient gave an 11-year history of recurrent carcinoma in situ in the anogenital area with eventual development of invasive cancer in the perirectal tissues, as noted in Cases 1 and 2. The past history was remarkable only for recurrent asthmatic attacks and frequent infections of the urinary tract. Specific therapy, such as steroids, has not been documented.

Case 4. M. V., a 76-year-old white woman, para 6-0-1-6, first presented in 1968, with an asymptomatic hyperkeratotic area on the posterior fourchette and an indurated urethral caruncle. Carcinoma in situ of the cervix had previously been diagnosed in 1961, and had been treated by a radical Wertheim hysterectomy. The vulvar lesion was excised, and pathologic examination demonstrated multifocal in situ carcinoma. In 1972, 4 years after the wide local excision, biopsies were repeated, confirming the presence of recurrent intraepithelial neoplasia (Fig. 5). Biopsy of a lesion at the external urethral meatus, 2 years later, revealed invasive epidermoid carcinoma with vascular involvement. She was treated with cesium inserted within the urethra. Subsequently, a lymphangiogram suggested the presence of a positive lymph node in the right pelvis, and she received external-beam irradiation to the pelvis. Cystoscopy, 2 months after irradiation, revealed that the distal half of the urethra was replaced by necrotic tumor. Within 3 months, the residual external genital region was replaced by invasive squamous-cell carcinoma. The patient was treated by an anterior pelvic exenteration, and ileal loop. Pathologic examination revealed poorly differentiated carcinoma, with tumor to the surgical margins at the symphysis (Fig. 6). No further treatment was instituted and the patient died approximately 8 months postoperatively, 14 months after the initial diagnosis of invasive cancer.

Case 5. A. M., an 82-year-old white woman, presented in 1972, with a chief complaint of pruritus. Examination revealed white areas on the vulva. She was treated by simple vulvectomy. Histopathologic study revealed multifocal carcinoma in situ. More careful sectioning revealed early invasion with atypical maturation at the rete tips (Fig. 7). No further treatment was instituted, and the patient revealed no gross evidence of disease until September, 1976, 4 years after the vulvectomy, when she presented with a granular ulceration, 2 to 3 cm in diameter, on the vulva. Wide local excision was performed, and the sections revealed well-differentiated invasive squamous-cell carcinoma with unclear margins. A second excision was performed, followed by a 3-month course of external ir-



**Fig. 7.** Case 5. Malignant vulvar lesion originally diagnosed as in situ cancer. Patient died in 5 years from widespread local invasive cancer. Note atypical "pearl formation" at the rete tips. (Original magnification, ×135.)

radiation. One year later, a biopsy confirmed the presence of residual invasive cancer, and the patient died as the result of uncontrollable hemorrhage.

### Comment

The five cases reported in this review demonstrate important clinical and/or histopathologic features of the patient at risk for the development of invasive anogenital canal carcinoma after surgical therapy for in situ disease.

It must be emphasized that three of the five patients who demonstrated progression of in situ disease to invasive disease were in the late third or early fourth decade of life when the initial lesion was discovered. The initial treatment in two of the three was vulvectomy; only wide local excision was performed in the final case. Two patients had received local 5-fluo-

rouracil cream therapy (5% Efudex cream). The third patient was immunosuppressed, and recurrent disease at the anal orifice had been treated with irradiation. Consequently, the local vulvar disease was controlled by surgical therapy and/or chemotherapy. All three patients subsequently developed invasive cancer in the perianal area, thus suggesting that this skin is "the tissue at risk." Certainly, the immunosuppression was a significant factor in one case since, with elimination of this medication, there has been no recurrence in the subsequent 3 years. The role of irradiation as a carcinogen in Case 1 is questionable. Nevertheless, it is obvious that many years may elapse between discovery of the initial disease and the development of invasive cancer. It must be stressed that the latter did not appear in the vulva but in the perianal area!

Two patients in the eighth and ninth decades of life with vulvar in situ disease were initially treated, one each, by vulvectomy and wide local excision. Invasive cancer developed in both at the excisional area and within a period of 5 years postoperatively. Of significance in these cases is the unique histologic pattern characterized by abnormal maturation of the tissues with the formation of intraepithelial pearls at the rete tips. Individual cell anaplasia was not a feature in these cases, as it was in the younger patient.

In summary, the young patient treated for in situ neoplasia of the anogenital canal rarely develops invasive disease; but if such a sequence of events occurs, the malignancy appears at the anal orifice, probably because of the many irritants and traumas to which this area is subjected. One may speculate that this critical "transformation zone" at the anal orifice responds to viral agents with atypical proliferations similar to those seen at the cervical os. The common finding of condylomata acuminata in association with neoplasia of the anogenital canal supports this thesis.

In Case 1, the area was also subjected to irradiation, a known skin carcinogen, and the patient was immunosuppressed as the result of long-term steroid therapy, thus adding another "at-risk factor" to the equation.

Finally, and most importantly, the physician must maintain a *high degree* of suspicion in the follow-up of these patients, local irritants must be removed, and biopsy examination must be used freely.

### REFERENCES

- Gardner, H. L., Friedrich, E. G., Kaufman, R. H., and Woodruff, J. D.: The vulvar dystrophies, atypias, and carcinomata in situ, J. Reprod. Med. 17:133, 1976.
- Woodruff, J. D., and Baens, J. S.: Interpretation of atrophic and hypertrophic alterations in vulvar epithelium, Am. J. Obstet. Gynecol. 86:713, 1963.
- 3. Kaufman, E. H., Gardner, H. L., and Brown, D. J.: Vulvar
- dystrophies, an evaluation, Am. J. OBSTET. GYNECOL. 120:263, 1974.
- Buscema, J., Genadry, R., Parmley, T., and Woodruff, J. D.: Carcinoma in situ of the vulva, Obstet. Gynecol. 55:225, 1980.
- Seski, T. C., Reinhalter, E. R., and Silva, T.: Abnormalities
  of lymphocyte transformation in women with intraepithelial carcinoma of the vulva, Obstet. Gynecol. 52:332, 1078.

### Carbohydrate metabolism with three months of low-estrogen contraceptive use

W. N. SPELLACY, M.D. W. C. BUHI, M.S. S. A. BIRK, R.N., B.S. Gainesville, Florida

Prospective studies of carbohydrate metabolism were performed by means of an oral glucose tolerance test in 29 women. The studies were performed before and after 3 months of treatment with an oral contraceptive that contained 0.035 mg of ethinyl estradiol and 0.4 mg of norethindrone. The 24 women with a "normal" control test had no significant alteration in any of their blood glucose and plasma insulin values, except that the fasting glucose level decreased with treatment. Three of these women (12.5%) had a slight deterioration of their glucose curves into a "borderline abnormal" grouping during treatment. There were five women with "borderline abnormal" control glucose curves, and in four of these (80%) the curves returned to "normal" during treatment, whereas one curve stayed "borderline abnormal." These data suggest that this low-estrogen oral contraceptive has minimal short-term adverse effects on the carbohydrate metabolism. (AM. J. OBSTET. GYNECOL. 138:151, 1980.)

DURING the past 15 years, many investigators have consistently noticed that the use of oral contraceptives (OC) has been associated with some alteration in carbohydrate metabolism.1 The usual findings were an increase in the levels of circulating plasma insulin and a smaller rise in the concentrations of blood glucose.1 The concern about these metabolic alterations was heightened when clinical studies suggested that women who were using the OC were at an increased risk for accelerated atherogenesis and premature myocardial infarction.2 Since most pharmacologic effects are related to dosage, it seemed reasonable to expect a lessened metabolic effect from the lower-dose drugs. Reported is a prospective study of carbohydrate metabolism in women who used one low-estrogen OC for 3 months.

> From the Department of Obstetrics and Graecology, University of Florida College of Medicine.

These studies were supported in part by a grant-in-aid from Mead Johnson & Company, Evansville, Indiana: Received for publication August 9, 1979.

Accepted December 10, 1979.

Reprint requests: W. N. Spellacy, M.D., Department of Obstetrics and Gynecology, The Abraham Lincoln School of Medicine, 840 South Wood St., Chicago, Illinois 60612.

### Methods

Twenty-nine volunteers who sought oral contraceptives from a family planning clinic agreed to participate in these studies. The procedures were explained to each patient, and all signed an informed consent approved by the University Committee for Human Experimentation. All of these women were at least 8 weeks post partum or had not been using steroid contraceptives for more than 3 months. They were all studied by means of an oral glucose tolerance test before starting to take the OC. Each was instructed to eat a diet high in carbohydrates (>250 grams per day) for the 3 days preceding the test, and they then reported to the metabolic laboratory at 0800 hours after having fasted for more than 10 hours. The women were weighed and then remained seated during the test. After a sample of antecubital blood had been drawn, the women drank a flavored solution containing 100 grams of glucose. Repeat samples of venous blood were drawn at 0.5, 1, 2, and 3 hours.

A portion of the blood was placed into tubes that contained sodium fluoride and potassium oxalate and mixed well; later, the glucose content was determined in duplicate by the method of Nelson and Somogyi.<sup>3, 4</sup> The other portion of the sample of blood was placed in tubes that contained heparin, and was mixed and centrifuged; the plasma was separated and immediately

**Table I.** Blood glucose values in "normal" women before and after 3 months of treatment with low-estrogen oral contraceptive containing 0.035 mg of ethinyl estradiol and 0.4 mg of norethindrone (N = 24)

		Control test (mg/dl)				Three-month test (mg/d!)				
	Fasting	0.5 hr	1 hr	2 hr	3 hr	Fasting	0.5 hr	1 hr	2 hr	3 hr ·
Mean	72.5	116.3	110.1	90.0	71.7	66.3	116.8	113.4	38.5	67.6
SEM t	$\frac{1.8}{2.499}$	4.2 0.072	$\frac{4.4}{0.422}$	3.8 0.267	$\frac{3.7}{0.656}$	1.6	5.2	6.2	4.1	4.8
Þ (	< 0.03	NS*	NS	· NS	NS-					

<sup>\*</sup>NS indicates not significant.

**Table II.** Plasma insulin levels in "normal" women before and after 3 months of treatment with low-estrogen oral contraceptive containing 0.035 mg of ethinyl estradiol and 0.4 mg of norethindrone (N = 24)

		Control test ( µunits/ml)						Three-month test ( µunits/ml)				
· .	Fasting	0.5 hr	1 hr	2 hr	3 hr	Fasting	0.5 hr	1 hr	2 hr	3 hr		
Mean	24.7	106.1	132.7	103.6	69.9	27.7	135.6	127.9	135.6	65.8		
SEM t	$\frac{2.3}{0.782}$	11.2 1.742	12.6 0.276	9.5 1.795	7.2 0.363	3.1	12.7	12.1	15.1	. 8.5		
р -	NS*	· NS	NS	· NS	, NS							

<sup>\*</sup>NS indicates not significant:

**Table III.** Blood glucose values in "borderline abnormal" women before and after 3 months of treatment with low-estrogen oral contraceptive containing 0.035 mg of ethinyl estradiol and 0.4 mg of norethindrone (N = 5)

		Three-month test (mg/dl)								
	Fasting	0.5 hr	1 hi	2 hṛ	. 3 hr	Fasting	0.5 hr	1 ḥr	2 hr	3 hr
Mean SEM t	75.0 4.8 0.603 NS*	111.2 14.3 0.868 NS	149.2 13.9 1.359 NS	140.0 11.2 2.812 <0.03	94.2 12.3 1.339 NS	70.4 5.9	125.8 8.3	122.2 14.2	94.8 11.5	73.2 9.7

<sup>\*</sup>NS indicates not significant.

frozen at  $-20^{\circ}$  C. Later, all of the samples from the two tests were assayed in duplicate for their insulin content by means of a modified solid-phase radioimmunoassay procedure.<sup>5.</sup> <sup>6\*</sup> This eliminated any interassay variability.

After the test the women were given oral contraceptive tablets and instructed in their use.† Previous findings by history, physical examination, and Papanicolaou smear had been normal in all of the women. They were then rescheduled to return to the metabolic laboratory for an identical repeat test on the twentieth

day (18 to 21) of their third cycle of OC treatment. • Each woman served as her own control with a predrug and a 3-month postdrug test, thus giving matched-pair data. All of the results were placed on punch cards and appropriately analyzed with the aid of a computer. Calculations were made of the means, standard deviations, standard errors of the means, and Student's t test values. The probability values were taken from two-tailed tables, and only values less than 0.05 were considered to be significant.

The women were divided into two subgroups on the basis of the results of the predrug glucose tolerance test. The pretreatment control test was interpreted on the basis of the Wilkerson Point Score (WPS) system, which is one method of determining the normal glucose tolerance test. According to that system, each point on the glucose test is given a numerical value.

<sup>\*</sup>The human insulin standard used in these assays was Lot No. 516-734-B33 supplied by Dr. Mary A. Root, of Lilly Research Laboratories, Indianapolis, Indiana.

<sup>†</sup>The drug Ovcon-35, containing 0.035 mg of ethinyl estradiol and 0.4 mg of norethindrone, was generously supplied by Mead Johnson Laboratories, Evansville, Indiana.

**Table IV.** Wilkerson Point Scores from the oral glucose tolerance tests on women before and after 3 months of treatment with low-estrogen oral contraceptive containing 0.035 mg of ethinyl estradiol and 0.4 mg of norethindrone (N = 5)

	Total Wilkerson Point Score									
Patient	Control test		Three-month test							
1,	0.5		0							
2 .	0.5		0							
3	0.5		1.0							
4 4	1.0		0							
- 5	1.5		0							
Mean	. 0.8		0.2							
SEM	0.2		0.2							
t	1.213		·							
р	. Not significant		·							

Fasting glucose values greater than 110 mg/dl are given 1.0 point, 1-hour values greater than 170 mg/dl are given 0.5 point; 2-hour values greater than 120 mg/dl are given 0.5 point; and 3-hour values greater than 110 mg/dl are given 1.0 point. The total points for the curve are then added, and those curves with 0 point are considered "normal," those with 2 or more points are considered "abnormal," and those with 0.5 to 1.5 points are considered "borderline abnormal." In the original group of 29 women, there were 24 with "normal" control curves and five women with "borderline abnormal" curves. These were analyzed separately.

The characteristics of these women were similar to those of any family planning population. In the "normal" group, the mean age was  $22.1 \pm \text{SEM} \ 0.7$  years and the mean parity was  $1.2 \pm \text{SEM} \ 0.3$ . The mean control weight was  $133.6 \pm \text{SEM} \ 4.7$  pounds, and the mean 3-month weight was  $135.7 \pm \text{SEM} \ 5.5$  pounds, which was not significantly different (t = 0.288; p nor significant). Similar data were found in the "borderline abnormal" group. Thus, the mean age was  $24.8 \pm \text{SEM} \ 2.9$  years; mean parity was  $1.1 \pm \text{SEM} \ 0.4$ ; mean control weight was  $115.8 \pm \text{SEM} \ 4.8$  pounds; and mean 3-month weight was  $120.2 \pm \text{SEM} \ 5.0$  pounds (t = 0.637; p not significant).

### Results

### Normal women.

Glucose. The statistical studies of the blood glucose values are given in Table I, and the mean values are plotted in Fig. 1. It can be seen that there was only one significant change in the group data, and that was in the fasting glucose, which fell during therapy. By selection there were no Wilkerson points in the control test. There were three women in the 3-month test

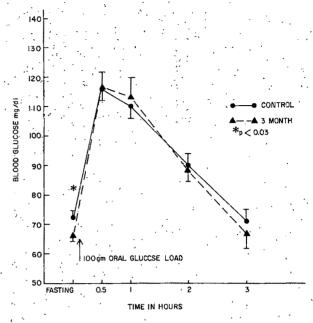


Fig. 1. Mean  $\pm$  SEM blood glucose values in milligrams per deciliter for "normal" women tested with an oral glucose tolerance test before and after 3 months of using an oral contraceptive containing 0.035 mg of ethinyl estradiol and 0.4 mg of norethindrone (N = 24).

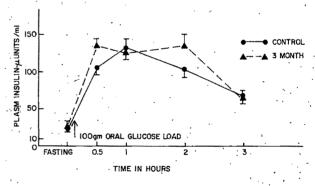


Fig. 2. Mean  $\pm$  SEM plasma insulin values in microunits per milliliter for "normal" women tested with an oral glucose tolerance test before and after 3 months of using an oral contraceptive containing 0.035 mg of ethinyl estradiol and 0.4 mg of norethindrone (N = 24).

(12.5%) who had WPS points which changed their glucose curve classification to "borderline abnormal" (WPS: 0.5, 1.0, and 1.0).

Insulin. The statistical studies of the plasma insulin values are given in Table II, and the mean values are plotted in Fig. 2. No significant changes were noticed during the 3 months of treatment.

### Abnormal women.

Glucose. The statistical studies of the blood glucose values for the two tests in this subgroup of women are

	Control test (µv:nits/ml)					Three-month test ( µunits/ml)				
,	Fasting	0.5 hr	1 hr	2 hr	3 hr	Fasting	0.5 hr	1 hr	2 hr	3 hr
Mean SEM	21.2 6.5	91.3 22.7	114.2 24.2	129.6 34.0	156.3 82.4	31.4	110.8 29.4	91.3 17.1	101.6 22.7	96.9 54.9
t D	1.065 NS*	0.525 NS	0.773 NS	0.684 NS	0.599 NS			.,		01.4

**Table V.** Plasma insulin values in "borderline abnormal" women before and after 3 months of treatment with low-estrogen oral contraceptive containing 0.035 mg of ethinyl estradiol and 0.4 mg of norethindrone (n = 5)

given in Table III. The single significant change was a fall in the 2-hour glucose value during treatment. The WPS for the control and 3-month tests are listed in Table IV. It should be noticed that for four of the five women (80%) the 3-month test reverted to "normal" during treatment, whereas for one the test remained "borderline abnormal" at 3 months.

Insulin. The statistical studies of the plasma insulin values are given in Table V. There were no significant alterations during therapy.

### Comment

The metabolic alterations which have accompanied the use of oral contraceptives have been a serious concern to many because of their potential to accelerate or initiate disease processes. 1-2 In order to avoid these problems, three types of research programs have been developed: identification of women at greatest risk; development of new contraceptive steroids which might be free of these adverse effects; and reduction of the dose of the classic contraceptive steroids to a level at which pregnancy is still prevented but at which adverse effects are minimal or eliminated. The latter approach has resulted in the production of a large group of oral contraceptives with less than 50 micrograms of estrogen which have been termed the "sub-50" or "lowestrogen" OC. Although clinical studies have demonstrated their effectiveness in preventing pregnancy,8 little data on their toxicity have been reported.

Few studies have been published on the effects of the low-estrogen OC on carbohydrate metabolism. Wynn and associates<sup>9</sup> studied 34 women before and after 3 months of use of a product with 30 micrograms of ethinyl estradiol, and noticed no change in glucose, although the levels of insulin became elevated.<sup>9</sup> A similar finding was made by Hausmann and colleagues.<sup>10</sup> Briggs and Briggs<sup>11</sup> evaluated 33 women who took a preparation which contained 30 micrograms of ethinyl estradiol for more than six cycles, and found no alteration in the fasting levels of blood glucose or plasma

insulin. All of these studies made use of the progestogen norgestrel.

Preliminary studies from this laboratory in another group of women who used 0.035 mg of ethinyl estradiol and 0.4 mg of norethindrone demonstrated a decrease in the 1-hour glucose value after 6 months, whereas the levels of plasma insulin were unchanged.<sup>12</sup>

The present studies extend and expand the earlier data on the effects of the low-estrogen type of oral contraceptives on carbohydrate metabolism. In this study, 29 women were treated for 3 months with a drug which contained 0.035 mg of ethinyl estradiol and 0.4 mg of norethindrone. Prospective studies were performed by means of a standard 3-hour oral glucose tolerance test with measurements of the levels of both blood glucose and plasma insulin. The results showed that women with "normal" carbohydrate tolerance had no deterioration in the values of blood glucose or plasma insulin, and, indeed, the fasting blood glucose value significantly decreased with therapy. The five "borderline abnormal" control curves generally improved with treatment. These results are different from those in women treated with oral contraceptives that contained 50 micrograms or more of estrogen, in which the values for both blood glucose and plasma insulin tended to increase during treatment.1

Even though these studies are only short term and on small numbers of women, they are encouraging, for they suggest that at least some of the important adverse metabolic secondary effects may be reduced or eliminated with some of the new OC preparations. This may have an effect on the clinical morbidities, such as vascular atherogenesis. Longer follow-up studies with larger groups of women are now needed with this and other low-estrogen OC preparations in order to confirm or refute these findings.

We wish to thank Mrs. M. Roundtree for her help in these studies, and Ms. E. Wells for her assistance in preparing the manuscript.

<sup>\*</sup>NS indicates not significant.

### REFERENCES

- 1. Spellacy, W. N.: Carbohydrate metabolism in male infertility and female fertility-control patients, Fertil. Steril. 27:1132, 1976.
- 2. Mann, J. I., Vessey, M. P., Thorogood, M., and Doll, R.: Myocardial infarction in young women, with special reference to oral contraceptive practice, Br. Med. J. 2:241,
- 3. Nelson, N.: Photometric adaptation of Somogyi method for determination of glucose, J. Biol. Chem. 153:375,
- 4. Somogyi, M.: Determination of blood sugar, J. Biol. Chem. 160:69, 1945.
- 5. Goetz, F. C., Greenberg, B. Z., Ells, J., and Meinert, C.: A simple immunoassay for insulin: Application to human and dog plasma, J. Clin. Endocrinol. Metab. 23:1237,
- 6. Herbert, V., Lau, K., Gottlieb, C. W., and Bleicher, S. J.: Coated charcoal immunoassay of insulin, J. Clin. Endocrinol. Metab. 25:1375, 1965.
- Wilkerson, H. C. L.: Diagnosis: Oral glucose tolerance tests, in Danowski, T. S., editor: Diabetes Mellitus: Diag-

- nosis and Treatment, New York, 1964, American Diabetes Association, Inc., pp. 31-34.
- 8. Sartoretto, J. N., Ortega-Recio, J. C., Moraes, R., and Filho, F. N.: Clinical studies with a low dose estrogenprogestogen combination, Contraception 15:563, 1977.
- Wynn, V., Adams, P., Oakley, N., and Seed, M.: Metabolic investigations in women taking 30 µg ethinyl estradiol plus 150 µg D-norgestrel, Excerpta Medica International Congress Series 344:47, 1974.
- 10. Hausmann, L., Goebel, K. M., Klähn, D., and Kaffarnik, H.: Insulin-und proinsulin-sekretion bei anwendung ant: Konseptioneller steroide, Klin. Wochenschr. 53:853,
- 11. Briggs, M. H., and Briggs, M.: Clinical and biochemical investigations of an ultra low-dose combination type oral contraceptive, Curr. Med. Res. Opin. 3:618, 1976.
- 12. Spellacy, W. N., Newton, R. E., Buhi, W. C., and Birk, S. A.: The effects of a "low-estrogen" oral contraceptive on carbohydrate metabolism during six months of treatment: A preliminary report of blood glucose and plasma insulin values, Fertil. Steril. 28:885, 1977.

### The effect of copper on spermatozoal motility and viability evaluated objectively with the aid of the multiple-exposure photography method

AMNON MAKLER, M.D. OREN ZINDER, Ph.D. Haifa, Israel

The antispermatozoal effect of the copper intrauterine contraceptive device (IUD) was investigated in an attempt to explain one aspect of its contraceptive mechanism. For this purpose, 42 specimens of normal semen were incubated in vitro with the metallic portion of two types of copper IUDs for 24 hours. Periodic determinations of sperm velocity and percentage of motility and viability were performed objectively with the aid of the multiple-exposure photography (MEP) method. No significant effect concerning these parameters was found when specimens were incubated continuously with either type of these IUDs at 23° C. On the contrary, sperm velocity and percentage of motility dropped markedly, and the number of dead spermatozoa increased reciprocally when specimens were incubated with those IUDs at 37° C for 4 hours. However, motility was almost unaffected in specimens that were incubated at 37° C with amounts of copper that exist usually within uterine cavities bearing this sort of IUD. The conclusion was that a copper IUD does not seem to exert its contraceptive effect by inhibiting spermatozoal activity. (Am. J. OBSTET. GYNECOL. 138:156, 1980.)

THE EXACT MODE of action of the inert intrauterine contraceptive device (IUD) is still not fully understood, nor is that of the copper IUD. The higher efficiency of the latter, claimed by some authors, may be attributed to various mechanisms: interaction between this metal and some vital enzymes, such as carbonic anhydrase, within the endometrium, augmentation of the leukocyte exudation effect by the endometrium, impaired thymidine incorporation, estradiol binding, or glycogen metabolism of the endometrium induced by the copper, and, finally a direct deleterious effect on spermatozoal motility and viability. The effect of copper ions on sperm motility was investigated long before the use of this metal with IUDs. Similar studies in which spermatozoa were incubated with metallic cop-

From the Infertility Institute, Department of Obstetrics and Gynecology, Clinical Biochemical Department, Rambam Medical Center, Technion—Faculty of Medicine.

Received for publication January 4, 1980.

Revised March 17, 1980.

Accepted March 28, 1980.

Reprint requests: Amnon Makler, M.D., Department of Obstetrics and Gynecology, Rambam Medical Center, Technion—Faculty of Medicine, Haifa, Israel.

per8, 9 were undertaken shortly after this device was introduced. The results of these investigations showed adverse effects that varied from one study to another and ranged from mild to very dramatic. The difference between these results depended on technical variations, whether ions or metallic copper was used, whether unwashed or washed spermatozoa were incorporated into the study, and whether experiments were performed at room temperature or at 37° C. However, in most of these in vitro studies, the concentrations of copper were much above the actual in vivo levels within uterine cavities containing copper IUDs. It was shown by Larsson and Hamberger<sup>10</sup> that the concentration of this metal within uterine cavities bearing copper IUDs for months and years did not exceed 500 µg/100 ml. According to Hagenfeldt,11 the concentration of copper within the endometrial tissue under some circumstances did not exceed 170  $\mu$ g/100 ml, and that in cervical mucus not more than  $220 \,\mu\text{g}/100 \,\text{ml}$ . On the contrary, it was shown by Jecht and Bernstein9 that the concentration of copper in seminal fluid incubated in vitro with this device for about 4 hours ranged between 3,000 and  $4,000 \,\mu\text{g}/100 \,\text{ml}$ . Biologically, it would be more relevant if the effect of a copper IUD on spermatozoal motility

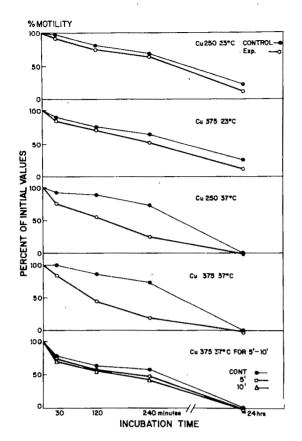


Fig. 1. Relative change in percentage of motility with time in specimens incubated at 23° C or 37° C with two types of copper IUDs, in comparison to the controls. Each point represents a mean value from eight to 10 specimens.

was investigated in vitro under conditions similar to those within a uterine cavity bearing that kind of IUD. In addition, in most of the previous studies, the asses= ment of sperm motility was based on subjective estimation, without any information on sperm velocity.

This common method is known to be very inaccurate and is of a very limited value for research studies. With the multiple-exposure photography (MEP) method which we recently developed,12 sperm motility and velocity can be analyzed objectively and accurately. This method was used in the present study to investigate the in vitro effect of metallic copper on sperm mobility and velocity, both at room temperature and at 37° C, and with steadily increasing amounts of copper as well as with low constant concentrations similar to those within the uterine cavity. The effect of this metal on sperm viability was investigated by combining the MEP and supravital staining methods. Thus, it became possible to conclude whether copper IUDs exerted their contraceptive effect directly on the sperm.

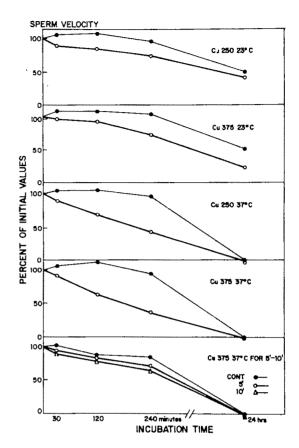


Fig. 2. Relative change in sperm velocity with time in specimens incubated at 23° C or 37° C with two types of copper IUDs, in comparison to the controls. Each point represents a mean value from eight to 10 specimens.

### Material and methods

Specimens of semen from 42 fertile donors were collected into glass vials by masturbation after 3 or 4 days of abstinence. Aliquots of normal saline solution, not more than 3 ml, were added, when necessary, to bring all specimens into a final volume of 6 ml. After being thoroughly mixed, each specimen was divided into two portions of 3 ml each and transferred into two narrow glass test tubes. The experimental test tube contained the metallic part, including the plastic core of multiload contraceptive copper IUD of either 250 or 375 type.\* The control test tube contained the plastic core only. All pieces were completely embedded within the seminal fluid. The following experiments, each one on a separate subgroup of specimens, were performed within 1 to 2 hours after ejaculation.

Experiment No. 1. Specimens that were incubated with either kind of copper devices, as well as their con-

<sup>\*</sup>Kindly supplied by Multilan SA, Fribourg, Switzerland.

Table I. Rates of sperm velocity and percentage of motility in eight specimens at various times after incubation with Cu-250 at 23° C as compared to controls

					Time of	incubation with	Cu-250 at 23° C	
	C4	Measure- ment	0	30	min	120 min		
Specimen No.	Sperm count (millions/ml)		Control and IUD	Control	IUD	Control	IUD	
1	97	%*	40	34	27	29	26	
		V†	45.6	39.5	30.1	38.0	25.9	
2	31	%	42	37	37	32	30	
		$\mathbf{v}$	33.0	30.9	27.3	26.6	23.1	
3	46	%	45	43	42	38	37	
		V	31.0	31.1	25.8	26.2	21.7	
. 4	63	%	66	62	63	58	57	
		V	31.2	40.3	31.2	45.0	40.4	
5	51	%	46	49	52	39	40	
		V	27.9	25.8	22.9	22.0	21.8	
6	37	%	55	52	46	38	35	
		V	35.9	42.0	36.0	40.4	38.6	
7	87	%	35	33	36	25	25	
•		V	31.5	32.4	31.1	37.7	26.3	
8	80	%	45	55	51	43	38	
-		$\mathbf{v}$	26.2	32.6	31.5	32.6	24.6	
Av ± SEM‡	62	%	$47 \pm 3.8$	$46 \pm 3.7$	$44 \pm 4.0$	$38 \pm 3.6$	$36 \pm 3.6$	
		V	$32.8 \pm 2.2$	$34.3 \pm 2.0$	$29.5 \pm 1.4$	$33.6 \pm 2.8$	$27.8 \pm 2.6$	
P values		%			NS§		< 0.05	
		v			< 0.01		< 0.01	
Cu concentration (µg/100 ml) Av ± SD			30		510 ± 107		$1,625 \pm 215$	

<sup>\*</sup>Percent of motile spermatozoa.

Table II. Rates of sperm velocity and percentage of motility in eight specimens at various times after incubation with Cu-375 at 23° C as compared to controls

			,		Time of i	incubation with	Cu-375 at 23° C	
			0	30	min	12	0 min	
Specimen No.	Sperm count (millions/ml)	Measure- ment	Control and IUD	Control	IUD	Control	IUD	
1	42	%	35	32	27	27	24	
		v	22.7	23.7	20.5	26.4	25.3	
2	76	%	68	52	53	48	48	
_		v	25.2	27	25.0	28.1	26.7	
3	91	%	. 69	68	66	60	51	
		v	35.7	39.7	34.9	37.5	29.4	
4	113	%	43	43	39	33	36	
		v	33.4	38.8	35.6	37.6	29	
5	41	%	38	34	22	27	24	
		v	29.2	31.6	28.4	32.1	27.6	
• 6	36	%	41	36	38	30	30	
_		v	30.6	32.0	30.2	31.8	29.6	
7	57	%	. 56	51	46	42	37	
·		$\tilde{\mathbf{v}}$	31.8	34.1	30.6	35.8	29.8	
8	32	%	39	34	35	28	30	
		$\ddot{\mathbf{v}}$	33.2	36.8	32.7	35.9	31.1,	
$Av \pm SEM$	61	%	$49 \pm 5.1$	$44 \pm 4.4$	$42 \pm 4.5$	$37 \pm 4.3$	$35 \pm 3.6$	
		V	$30.4 \pm 1.9$	$29.7 \pm 1.8$	$33.0 \pm 2.0$	33.2 = 1.5	$33.0 \pm 1.5$	
Av P values		% V			NS		NS	
		v			< 0.001		< 0.01	
Cu concentration			30		$1,035 \pm 81$		$1,622 \pm 150$	
$(\mu g/100 \text{ ml})$								
$Av \pm SD$						,		

SD = Standard deviation.

<sup>†</sup>Average velocity in microns per second.

<sup>§</sup>NS = Not significant.

<sup>‡</sup>SEM = Standard error of mean.

24	0 min		24 hr
Control	IUD	Control	IUD
25 31.9 26 26.3 32 24.0 54 44.6	23 21.1 24 22.6 31 20.0 49 33.1	13 16.3 0 0 3 15.0 31 28.5	13 19 0 0 3 23.3 4 20.0
$36$ $21.3$ $32$ $40.4$ $19$ $31.4$ $39$ $35.0$ $33 \pm 3.8$ $31.9 \pm 2.8$	$34$ $23.5$ $27$ $31.1$ $23$ $23.2$ $34$ $26.6$ $31 \pm 3.1$ $25.2 \pm 1.7$ $NS$ $< 0.01$ $2,759 \pm 265$	$5 \\ 20.0 \\ 7 \\ 16.6 \\ 7 \\ 20.0 \\ 23 \\ 19.7 \\ 11 \pm 3.8 \\ 17.0 \pm 2.8$	5 10.0 2 10.0 10 15.4 3 13.5 5 ± 1.5 13.9 ± 2.6 NS NS 14,220 ± 758

	24	0 min	<u> </u>	24 hr
	Control	IUD	Control	IUD
	26	15	0	0
•	22.4	17.7	0	0
	34	30	8	0
	34.1	20.4	31.0	. 0
	50	41	40 -	26
	33.6	28.4	26.9	23.6
	28	22	14	6
	33.0	20.4	16.0	10.0 -
	21	18 .	0	. 0
	29.8	21.6	0	0
	. 26	23	16	6
	30.6	24.3	19.8	10.1
	36	31	12	5
	33.3 °	24.1	17.2	9.3
	23	23	15	8
	34.1	23.8	21.0	6.2
	$31 \pm 3.3$	$25 \pm 3.0$	$13 \pm 4.4$	$6 \pm 3.0$
_	$31.4 \pm 1.4$	$22.6 \pm 1.2$	$16.5 \pm .1.2$	$7.4 \pm 2.8$
-		< 0.01		< 0.01
		< 0.001		< 0.05
		$2,135 \pm 158$		$12,550 \pm 365$

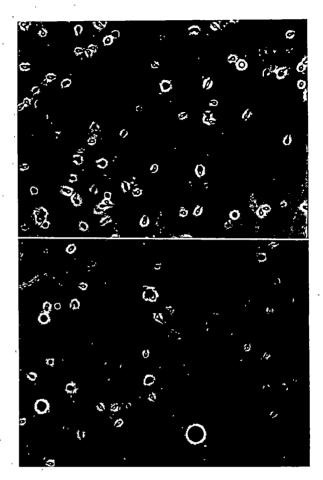


Fig. 3. Photomicrographs of two samples of the same specimen taken with the MEP method after being incubated at 37° C for 4 hours. A, Experimental sample, incubated with copper IUD. B, Control sample, incubated with the plastic core only. Note the lesser abundance of motile spermatozoa seen as sixringed chains in the experimental sample. The higher percentage of nonmotile spermatozoa, appearing as accentuated images, is evident.

trols, were kept at room temperature. Sperm motility and concentrations of copper were determined periodically for the following 24 hours.

Experiment No. 2. Specimens incubated with either kind of copper devices, as well as their controls, were kept at 37° C. Sperm motility and concentrations of copper were determined as before.

Experiment No. 3. To investigate the effect of copper at levels of concentration that are similar to those existing in the uterine cavity containing this kind of device, specimens were incubated at 37° C with Cu-375 IUDs for 5 or 10 minutes. Then the devices were removed and the specimens were incubated for the remainder of the 24 hours only with the amount of copper that had been released up to that moment. Sperm motility and concentration of copper were assessed as before. These time durations of 5 and 10 minutes were

**Table III.** Rates of sperm velocity and percentage of motility in eight specimens at various times after incubation with Cu-250 at 37° C as compared to controls

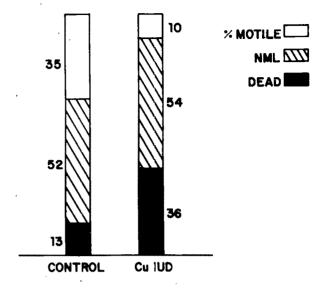
		1	,		Time of	incubation with	Cu-250 at 37° C
	Sperm count (millions/ml)	Measure- ment	0	30 min		120 min	
Specimen No.			Control and IUD	Control	IUD	Control	IUD
1	52	%	43	41	35	40	27
		V	32.3	34.6	29.3	35.3	24.1
2	76	% V	68	65	48	66	44
		v	35.1	37.2	31.1	33.1	26.7
3	34	%	72	69	56	65	41
		% V	28.7	23.2	25.6	32.3	19.8
4	126	% V	56	51	43	47	30
		V	29.3	33.1	28.1	34.7	22.6
5	28	% V	51	49	41	45	. 28
		V	31.6	34.1	29.0	33.6	34.7
· 6	47	% V	40	37	30	38	22
		v	30.8	30.9	27.3	32.7	18.7
7	61	%	38	38	31	32	23
		V	27.9	28.7	22.6	27.1	15.6
8	42	. %	48	44	34	40	21
*		V	33.1	33.0	30.2	34.6	24.2
$v \pm SEM$	58	%	$52 \pm 5.0$	$49 \pm 4.2$	$40 \pm 3.2$	$47 \pm 4.0$	$30 \pm 3.1$
		v	$31.1 \pm 1.3$	$32.5 \pm 1.1$	$27.9 \pm 1.0$	$32.9 \pm 0.9$	$21.9 \pm 1.3$
v P values		. %			< 0.001		< 0.001
		. <b>%</b> <b>V</b>	*		< 0.001		< 0.001
Cu concentration (μg/100 ml) Av ± SD	·	,	30	•	$2,123 \pm 607$		$3,289 \pm 230$

**Table IV.** Rates of sperm velocity and percentage of motility in eight specimens at various times after incubation with Cu-375 at 37° C as compared to controls

			,	•	Time of in	cubation with	Cu-375 at 37° C	
·		Mea- surement	0	30 min		1	20 min	1
Specimen No.	Sperm count (millions/ml)		Control and IUD	Control	IUD	Control	IUD	
1	72	%	44	48	. 27	56	` 7	
		V	34.5	33.7	25.8	35.9	13.6	
2	46	%	49	50	36	42	7	
		V	27.5	32.5	27.6	38.4	11.5	
3	93	%	55	. 57	51	32	27	
		v	35.3	41.4	36.8	36.1	33.1	
4	38	%	80	85	- 73	83	- 65	
		v	36.4	37.1	36.6	39.7	34.2	
5	66	%	24	71	69	66	45	
		V	41.4	. 36.7	31.0	38.8	19.6	
6	53	%	46	50	35	39	14	
•		, V	23.3	29.6	17.3	31.7	14.5	
7	109	. V %	41	38	34	29	17	
		$\mathbf{v}$	29.3	31.6	29.3	32.6	19.2	
8	31	%	39	32	30	27	• 45	
		V	28.7	29.8	28.7	31.4	22.1	
$Av \pm SEM$	64	%	$54 \pm 6.9$	$54 \pm 6.1$	$44 \pm 6.3$	$47 \pm 7.0$	$25 \pm 7.2$	
		$\mathbf{v}$	$32.1 \pm 2.0$	$34.1 \pm 2.2$	$29.1 \pm 2.2$	$35 \pm 1.2$	$21.0 \pm 3.0$	
Av P values		% V			< 0.01		< 0.01	
		V			< 0.01		< 0.01	
Cu concentration (µg/100 ml) Av ± SD	$Av \pm SD$				$1,443 \pm 210$		$3,296 \pm 429$	

240	min		24 hr
 Control	IUD	Control	IUD
 36	10	0	0 .
31.6	15.7	0	0
58	14	0	0
34.2	12.3	0	0
50	18	0	0
29.2	10.5	0	0
34	11	0	0
28.7	14.3	0	0
41	14	0	0
30.7	13.2	0	0
31	18	0	0
29.8	19.8	0	0
23	. 15	0	0
27.2	10.0	0	0
31	13	0	0
32.6	11.2	0	0
$38 \pm 4$	$14 \pm 1.0$	0	0
$30.5 \pm 0.8$	$13.4 \pm 1.1$ $< 0.001$ $< 0.001$	0	0
	$4,986 \pm 903$		$28,740 \pm 2,115$

	240	0 min		24 hr
,	Control	IUD	Control	IUD
	20	1	0	0
	35.1	10.9	0	0
•	46	0	0	0
	34.1	0	0	0
	23	18	0	0
	26.6	19.5	0	0
	70	45	0	0
	32.8	23.2	, 0	0
	65	7	0	0
	29.4	13.8	0	0
	33	1	0	0
	23.4	10.0	0	0
	26	10	0	0
	29.6	13.2	0	0
	23 •	7	0	0
	30.6	10.2	. 0	0
	$40 \pm 6.7$	$11 \pm 5.3$	0	0
	$30.2 \pm 1.4$	$12.5 \pm 2.5$	0	0
		< 0.01		
•		< 0.01		
		$4,029 \pm 765$		$22,356 \pm 1,$



### AFTER 4 HOURS AT 37°C

Fig. 4. Ratio of motile, nonmotile-live (NML), and dead spermatozoa as determined by the combined MEP and supravital staining methods in eight specimens incubated with copper IUDs at 37° C for 4 hours, as compared to the controls.

selected according to our preliminary findings on the amount of copper released from these IUDs, which slightly exceeded that found within uterine cavities by Larsson and Hamberger<sup>10</sup> and Hagenfeldt.<sup>11</sup>

Determination of concentration of copper. In all of these experiments, copper was assayed by atomic absorption spectrometry, with the use of the Varian Mode 1200.

Assessment of motility. Motility was assessed by the MEP method, as previously described. 12, 13 Each of two or three drops from a well-mixed specimen was placed in a special 10  $\mu$  chamber,\* and four to six fields that contained 200 to 400 spermatozoa were photographed at predetermined locations. In each instance the film was exposed for 1 second, during which time the sample was illuminated by six light pulses. Images of photographed spermatozoa were projected onto sheets of paper, and from these the percentage of motile spermatozoa and their velocity were calculated as described.

In those cases in which motility was significantly affected by the presence of copper, sperm viability was also analyzed, by a combination of supravital staining and the MEP method, as described previously.14 Each sample was mixed with 1% eosin-Y for 2 minutes and photographed as described, with the use of a green

\*Manufactured by EL-OP, the Israel Electrooptic Industry, Rehovoth, Israel.

**Table V.** Rates of sperm velocity and percentage of motility in 10 specimens incubated with copper ions released from the IUD during the first 5 or 10 minutes before being removed from the test tube

					Time of incub	ation with Cu-3	75 for 5 or 10	nin at 37° C
		,	0		30 min			120 min
Specimen No.	Sperm count (millionstml)	Mea- surement	Control and IUD	Contrel	5 min	10 min	Control	5 min
1	. 47	%	38	49	47	58	42	49
		V	29.6	34.6	31.5	28.8	31.4	27.5
2	52	%	40	43	43	36	38	44
		V	34.0	34.9	31.2	32.9	30.6	30.4
3	29	%	36	22	24	24	29	17
		V	26.9	25.7	21.8	26.4	31.3	26.6
4	56	%	42	15	15	22	. 17	15
		V	23.1	23.7	23.4	18.7	20.2	19.1
5	93	%	65	49	41	36	31	31
		V	38.7	38.⊊	34.1	31.5	29.2	29.2
6	67	%	43	32	32	31	32	30
		v	28.9	26.€	28.6	26.4	25.9	17.5
7	. 56	%	51	44	36	47	40	33
		v	22.7	24.0	20.8	21.4	23.3	20.9
8	83	%	42	27	23	19	11	6
		v	28.4	18.€	20.5	25.6	16.5	15.3
9	72	%	28	21	19	24	14	24
		v	28.9	34.8	24.4	24.2	28.5	31.7
10	139	%	45	36	26	28	13	4
-		v	30.3	30.C	26.2	25.5	16.2	18.6
v ± SEM	69	%	$43 \pm 4.1$	$34 \pm 5.9$	$31 \pm 3.4$	$33 \pm 3.9$	$27 \pm 3.8$	$25 \pm 4.7$
		v	$28.9 \pm 1.8$	$29.1 \pm 2$	$26 \pm 1.5$	$26.1 \pm 1.4$	$25.3 \pm 1.9$	$23.7 \pm 1.9$
v P values		- %	,		< 0.05	NS		NS
		. <b>v</b>			< 0.05	NS		NS
u concentration (μg/100 ml) Av ± SD					577 ± 112	926 ± 247		577 ± 112

filter and color slides. From projected images, the ratio between dead spermatozoa (red stained), nonmotile-live spermatozoa (unstained, appearing green), and motile spermatozoa (chains) was simultaneously determined.

Results from all experiments were evaluated statistically, and significance was determined by means of the paired t test.

### Results

Tables I through V demonstrate the change in sperm velocity and percentage of motility with time in all 42 experimental and control specimens, subgrouped according to the described experiments. The corresponding amounts of copper released into the fluid contained within the test tube are shown as well. Figs. 1 and 2 reveal graphically the mean relative change of these parameters with time in experimental and control specimens. It can be seen that sperm velocity and percentage of motility in specimens incubated at room temperature with either type of IUD showed a pattern of change with time almost like that in control samples and similar to that in normal specimens, as

described previously.<sup>15</sup> However, the patterns of experimental specimens differed significantly from those of the controls when incubated at 37° C, and sperm velocity and percentage of motility dropped markedly with the continuous presence of copper within the specimens in the test tubes. This drop was basically the same whether the specimens were incubated with Cu-250 or Cu-375 devices, as were the amounts of copper released from both kinds of IUDs. These amounts of copper were higher than those released by both kinds of IUDs at 23° C at identical times.

When incubated at 37° C with low and constant amounts of copper, released during the first 5 or 10 minutes of incubation, the changes in sperm motility and velocity with time did not differ significantly from those in control specimens. These amounts, 500 or 900  $\mu$ g/100 ml, respectively, were much below those released during continuous presence of an IUD, which reached 14,000  $\mu$ g/100 ml at 23° C and 24,000  $\mu$ g/100 ml at 37° C. No motile spermatozoa could be found after 24 hours in any of the specimens kept at 37° C, whether incubated or not with copper IUDs.

Fig. 3 shows photomicrographs of one of the speci-

•			240 min	-
	10 min	Control	5 min	10 min
	36	33	28	33
	28.0	28.6	22.2	20.3
	34	44	37	25
	20.3	23.8	23.7	17.5
	28	18	8	19
	28.8	33	25.5	13.7
	20	16	12	14
	19.1	22.6	20.0	15.8
	33	36	25	23
	29.2	24.7	22.7	23.2
	25	23	23	20
	17.5	16.8	19.6	16.3
	36	43	29	33
	20.9	24.4	20.1	20.4
	. 8	14	6	8
	15.3	17.0	22.3	13.1
	17	19	9	18
	31.7	36.5	30.0	25.7
	9	. 8	0	2
	18.6	22.2	.0	10.0
	$25 \pm 3.4$	$25 \pm 4$	$18 \pm 3.9$	$20 \pm 3.1$
2500	$22.9 \pm 1.9$	$25.0 \pm 2.0$	$20.6 \pm 2.5$	$17.6 \pm 1.6$
	NS		< 0.001	< 0.05
	NS	•	NS	< 0.01
	$926 \pm 247$		$577 \pm 112$	$926 \pm 247$

mens after 4 hours of incubation at 37° C, taken with the MPE method. Motile spermatozoa, seen as sixringed chains, are less abundant and the lengths of their chains, representing their velocity, are shorter in the experimental sample (A) than in the control sample (B). On the contrary, the relative number of nonmotile spermatozoa, seen as accentuated images, is higher in the experimental specimen.

The histograms in Fig. 4 are based on the results obtained from the combined supravital staining and the MEP methods, and show the ratio between motile, nonmotile-live, and dead spermatozoa in specimens incubated at 37° C for 4 hours with both kinds of copper IUDs, as compared to the controls. The decrease in motile spermatozoa and increase in dead spermatozoa under the influence of copper was found to be significant, whereas the percentages of nonmotile-live spermatozoa are roughly the same in both groups.

### Comment

The results of this study clearly demonstrated how the effect of copper on sperm motility varied according to the conditions under which the experiments took place, and was dependent on the temperature and concentration of copper at which spermatozoa were incubated. High concentrations of copper markedly decreased sperm velocity and percentage of motility only at 37° C. However, at concentrations that were close to those within uterine cavities containing copper IUDs, no significant effect on sperm motility, even at body temperature, could be found. The harmful effect of copper which, in our study, was related to its concentration and temperature of incubation is in accord with findings reported by others and can explain the results of a mild effect at room temperature in contrast to a striking effect at body temperature. Whether this effect was augmented through the higher amounts or copper released at body temperature, or was due to aggravation of copper toxicity at this temperature, needs more investigation. However, it seems reasonable to assume that high temperature per se contributes its effect in some biologic way other than by just increasing the release of copper: at room temperature, motility was not much affected and, surprisingly, motile spermatozoa existed after 24 hours of incubation within some deeply blue-colored specimens with a copper concentration as high as  $14,000 \mu g/100 \text{ ml}$ . On the contrary, a marked drop in sperm motility occurred with lower concentrations of copper when incubated at 37° C. The absence of motile spermatozoa in both experimental and control specimens after 24 hours of incubation at 37° C was the result of an enormous growth of a bacterial population that was disclosed by direct microscopic observation of all these specimens.

The toxic effect of copper in specimens incubated continuously with increasing amounts of these ions at 37° C was clearly illustrated in the results obtained from the combined MEP and supravital staining techniques. The relative increase in dead spermatozoa that accompanied the decrease in motile spermatozoa points to the toxic-spermicidal effect of copper, in addition to its motility-inhibitory effect. This toxic effect of copper which has already been described by others was attributed to its sulfhydryl-binding properties. 7 It is well known that sulfhydryl is an essential component of some vital enzymes. This assumption was supported by the findings that this deleterious effect was partially neutralized by the addition of chelating agents. 16

It seems to us that the most important findings of this study are provided by the results of Experiment No. 3, in which sperm motility was determined from specimens incubated at a temperature and a concentration of copper that are similar to those within uterine cavities containing these devices. It is obvious that the in vivo concentration of copper within the uterine cavity never reaches levels as high as those found when

these IUDs were placed into specimens in vitro. Copper cannot accumulate in the uterine cavity in the same way that it does in ordinary test tubes. Equilibrium between the level of copper within the uterine cavity and the levels in the body fluids is reached very quickly because of rapid absorption and distribution, and remains constant for months. 10, 11 Our findings that, under these circumstances, sperm motility and survival did not differ much from motility and survival in control specimens cannot support the theory that the copper IUD exerts its antifertility effect by inhibiting spermatozoal activity. Other investigators found that the motility of washed spermatozoa was markedly inhibited by similarly low concentrations of copper ions, presumably because the protective mechanism provided by the protein of the seminal fluid was lacking.8,9 However, this may not be the case in vivo, since proteins of the uterine fluid are supposed to possess this protective property in the same manner as does seminal fluid. In the study of Jecht and Bernstein, specimens were placed in Millipore chambers and kept for several hours within uterine cavities containing copper IUDs. The study showed that sperm motility was almost unaffected, which supports our findings in vitro. However, Jecht and Bernstein assumed that copper ions did not diffuse well enough into these chambers, but performed no assay. Even if copper did diffuse freely into these chambers, the concentration of it within the uterine cavity would not be high enough to inhibit sperm motility.

We wish to thank Dr. William A. A. VanOs, of the Department of Obstetrics and Gynecology, St. Elisabeth's of Groote Gasthius, Haarlem, Holland, for his encouragement in the carrying out of this study.

### REFERENCES.

- 1. Intrauterine devices, Series B-3, Publications of the Population Information Program, Baltimore, Maryland, May, 1977, p. 57.
- 2. Tatun, H. J.: Intrauterine contraception, Am. J. Obstet. Gynecol. 112:1000, 1972.
- Candros, A., and Hirsch, J. G.: Copper intrauterine devices stimulates leukocyte exudation, Science 175:175, 1979
- 4. Prager, R.: Effects of various types of intrauterine foreign bodies on the incorporation of \$-35 into mucoprotein and of thymidine 2-14C into DNA of rats endometrium, Fertil. Steril. 20:944, 1919.
- Nilson, O.: In Diczfalusy, E., and Bonel, U., editors: Nobel Symposium No. 15, Stockholm, Upsala, 1970, Almqvist & Wiksell, p. 216.
- Loeur, L. K.: Immobilization of human spermatozoa with iron. A basis for a new contraceptive, Contraception 3:219, 1971.
- MacLeod, J.: Sulfhydryl groups, lithium and the motility of human spermatozoa, Anat. Rec. 97:354, 1947.
- 8. Ullmann, G., and Hammerstein, J.: Inhibition of sperm motility in vitro by copper wire, Contraception 6:71, 1979
- 9. Jecht, E. W., and Bernstein, G. S.: Influence of copper on

- the motility of human spermatozoa, Contraception 7:381, 1973.
- Larsson, B., and Hamberger, L.: The concentration of copper in the human uterine secretion during four years after insertion of copper-containing intrauterine device, Fertil. Steril. 28:624, 1977.
- Hagenfeldt, K.: Intrauterine contraception with the copper-T device. 1. Effect on trace elements in the endometrium, cervical mucus and plasma, Contraception 6:37, 1972.
- Makler, A.: A new multiple exposure photography method for objective spermatozoal motility determination, Fertil. Steril. 30:192, 1978.
- Makler, A.: Use of the elaborated MEP method in routine sperm motility analysis and for research purposes, Fertil. Steril. In press.
- Makler, A.: Simultaneous differentiation between motile, nonmotile live, and dead spermatozoa by combining supravital staining and MEP procedures, Int. J. Androl. 2:32, 1979.
- Makler, A., Zaidise, I., Paldi, E., and Brandes, J. M.: Factors affecting sperm motility. I. In vitro change of motility with time after ejaculation, Fertil. Steril. 31:147, 1979.
- White, I. G.: Studies of the spermicidal activity of chelating agents, Aust. J. Biol. Sci. 7:379, 1954.

### SO EFFECTIVE YOU'D EXPECT TO WRITE A PRESCRIPTION

## SO SAFE YOU'T HAVE TO



Preparation H and its principal ingredient—Skin Respiratory Factor (SRF) have been studied in vitro.\* A group of world renowned wound-healing specialists confirmed that SRF stimulated wound oxygen consumption, epithelialization and collagen synthesis.

The unique Preparation H formula temporarily relieves pain and itching in many cases and actually helps shrink swollen hemorrhoidal tissue due to inflammation. All without anesthetics or steroids.

PREPARATION H

REPARATION

Helps shrink swelling of hemorrhoidal tissues...caused by inflammation and gives prompt, temporary relief in many cases from pain and itching in tissues.

NET WT. 2 OZ.

### PREPARATION H®

Clinically tested.

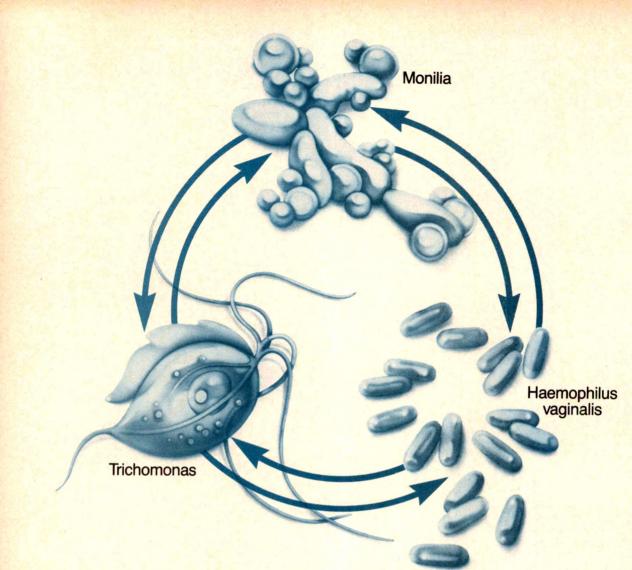
Available in ointment and suppositories.

PREPARATION H ACTIVE INGREDIENTS: Live Yeast Cell Derivative, supplying 2,000 units Skin Respiratory Factor Per Ounce of Base; Shark Liver Oil 3.0%, supplying Vitamin A.

\*Goodson W, Hohn D, Hunt TK, et al: Augmentation of some aspects of wound healing by a "Skin Respiratory Factor." *J Surg Res* 21:125-129, 1976.

For literature and patient education material, send coupon to Medical Dept., Whitehall Laboratories, 685 Third Avenue, New York, New York 10017.

AJOG 9/15.	
Please send	
Skin Respiratory Fa	ntation of Some Aspects of Wound Healing by a actor"
	polylote on the common courses provention and
	ooklets on the common causes, prevention and
Patient Education B treatment of hemor	
treatment of hemor	rhoids
treatment of hemor	rhoids
treatment of hemor	rhoids



### riple target therapy for infectious vaginitis BETADINE Microbicides Vaginitis Regimen

- Broad-spectrum microbicidal action kills all three pathogens usually responsible for infectious vaginitis—monilia, *Trichomonas* and *Haemophilus vaginalis*.
- Microbicidal action is maintained in the presence of blood, serum and vaginal secretions.
- Virtually nonirritating to skin and vaginal mucosa—nonstaining to skin and natural fabrics.

Easy-to-follow regimen
IN THE OFFICE
BETADINE® Solution

AT HOME BETADINE® Vaginal Gel\* (povidone-iodine)

### **BETADINE®** Douche

- In the office, swab the cervix and vulvovaginal area with BETADINE Solution.
- Prescribe BETADINE Vaginal Gel (povidone-iodine), one applicatorful of which is to be inserted each night.
- Followed the next morning by BETADINE Douche in therapeutic concentration— 2 tablespoonfuls to a quart of lukewarm water.
- After two weeks
  - —Patient returns for an office visit.
  - In more resistant cases, the regimen may be continued through 1 or 2 cycles, if necessary.

### \*BETADINE® Vaginal Gel

(povidone-iodine)

**Brief Summary** 

For use in the treatment of Trichomonas vaginalis vaginitis, monilial vaginitis and nonspecific vaginitis.

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: possibly effective for use in the management of trichomonas vaginalis vaginitis, monilial vaginitis and nonspecific vaginitis. Final classification of the less-than-effective indications requires further investigation.

### Precaution

If irritation, redness or swelling develops, discontinue use. The rare individual with history of iodine sensitization should not use this product, pending further investigation.

**Purdue Frederick** 

© 1980, The Purdue Frederick Company/Norwalk, CT 06856 218680 A9716

### Permanente

PC/PHYSICIANS & SURGEONS

### GROUP PRACTICE OPPORTUNITIES Pacific Northwest

Rapid membership growth has created an immediate opening in the Department of Obstetrics/Gynecology of Northwest Permanente, P.C. in Portland, Oregon. We are seeking obstetrician/gynecologists to join an active service with over 3,900 annual deliveries, a high risk intensive care nursery and complete fetal monitoring equipment.

Nortwhest Permanente, P.C. is a professional medical corporation which provides health care services to the 235,000 members of the Kaiser Foundation Health Plan of Oregon. Through its association with Kaiser Foundation Health Plan, a federally qualified HMO, Northwest Permanente, P.C. operates nine outpatient clinics and two full service hospitals.

The medical practice is varied and professionally stimulating offering the physician a pure practice free of business and administrative concerns. A comprehensive salary and benefits package including a sabbatical program, malpractice coverage, three weeks vacation and one week educational leave to start, life, medical/dental and disability insurance along with two excellent retirement programs is provided. The physician is eligible for ownership participation after two years.

Portland, Oregon, on the Columbia and Willamette Rivers, is a city with a moderate climate located in a stable, prosperous economic region of the beautiful Northwest. Outdoor recreational facilities are superb and include excellent skiing, backpacking, fishing and boating opportunities. The Environmental Protection Agency, in a recent study, selected Portland as the "most livable city" in the United States.

Please send two (2) copies of a curriculum vitae with your initial response to Marvin P. Goldberg, M.D. President, Northwest Permanente, P.C., 1500 S.W. 1st Avenue, 11th Floor, Portland, Oregon, 97201.

### NORTHWEST PERMANENTE, P.C. — PHYSICIANS & SURGEONS

An Equal Opportunity Employer

### OB/GYN

Prepaid medical group practice, established 1976. Two suburban care centers, each with 3 or 4 BC/BE OBG'S. New comprehensive facilities. Well-staffed for clinical support, including Nurse Practitioners and hospital residents. Attractive salary structure and liberal fringes. Starting salary based on experience. Recruitment and relocation expenses covered. Unusually livable city. Send CV or call: Michael R. Soper, M.D. Medical Director 6801 E. 117th Street Kansas City, Missouri 64134.

# Cardiotocograph for maximum information in gynecologic diagnostics

r.E. BIOMEDICA

### OBSTETRICS

### Plasma volume expansion in the treatment of pre-eclampsia

NARINDER N. SEHGAL, M.D. JOHN R. HITT, M.D. Charleston, West Virginia

The effects of plasma volume expansion with hyperosmo ar solutions with the use of dextran 40 and plasmanate were studied in a controlled manner in 32 pr miparous pre-eclamptic patients. The patients who were being studied received either dextran 40 (Rheomacrodex) or plasmanate in addition to the routine treatment with sedatives, bed rest and magnesium sulfate when indicated. The patients were randomly assigned by blind draw to control (13), dextran (10), and plasmanate (nine) groups. The renal status of all patients was evaluated prior to volume expansion therapy. Patients were monitored for blood pressure, proteinuria, output of urine, hematocrit, and creatinine clearance. There was significant improvement in hemoconcentration and output of urine, and a trend toward a lowering of the mean arterial blood pressure in patients who were receiving plasmanate or dextran for volume expansion. (Am. J. DESTET. GYNECOL. 138:165, 1980.)

PREGNANCY-INDUCED hypertension (pre-eclampsia) is an important cause of perinatal and material mortality and morbidity. Although the etiology of pre-eclampsia is still obscure, several pathophysiologic aspects of it are known. These include: arteriolar vasospasm that leads to hypertension, increased vascular reactivity, retention of sodium, decreased glomerular filtration rate, decreased blood volume, increased irritability of the central nervous system, and a negative nitrogen balance.<sup>1</sup>

That the blood volume in pre-eclamptic patients is decreased as compared to that in normal pregnant patients of comparable period of pregnancy is now generally accepted.<sup>2, 3</sup> Recently, some investigators<sup>4, 5</sup> have shown encouraging results with blood volume expansion therapy in these patients. Blood volume expansion

From the Department of Obstetrics and Gynecology, Charleston Division, West Virginia University Medical Center. and the Charleston Area Medical Center.

Received for publication April 21, 1980.

Accepted May 5, 1980.

Reprint requests: Narinder N. Sehgal, M.D., 3200 McCorkle Ave., S. E., Charleston, West Virginia 25304. therapy appears to reverse the disease process, at least temporarily, in a significant number of patients. However, controversy exists in regard to the beneficial effects and the wisdom of using such therapy.<sup>6</sup>

A prospective, randomized, controlled study was initiated at the Charleston Area Medical Center to study the effects of plasma volume expansion in pre-eclamptic patients. For volume expansion, plasmanate and low-molecular-weight dextran (Rheomacrodex\*) were used. Control patients received 5% dextrose solution in distilled water.

### Material and methods

Primiparous patients who were admitted to the Charleston Area Medical Center (CAMC), Memorial Division, with the diagnosis of pre-eclampsia, were invited to participate in the study, and an informed consent was obtained from each patient who agreed. Patients were randomly assigned by blind draw to the control, dextran, or plasmanate group. Patients with

\*Supplied by Pharmacia Laboratories, Piscataway, New Jersey.

**Table I.** Number of patients requiring magnesium sulfate therapy, being delivered of infants by cesarean section, and developing complications in the three study groups

	$\begin{array}{c} Control \\ (N=13) \end{array}$	Plàsmanate (N = 9)	Dextran (N = 10)
Magnesium sulfate	5	7	6
Cesarean section	4	3	6
Preterm delivery	3	2	4
Abruptio placentae	1	. 1	1
Perinatal deaths	0	1	1

cardiac disease, renal or pulmonary insufficiency, and severe pre-eclampsia, who required antihypertensive therapy and prompt termination of pregnancy, were not included in the study.

Diagnosis of pre-eclampsia was made by means of standard criteria of hypertension with proteinuria or generalized edema, or both, induced by pregnancy after the twentieth week of gestation. Hypertension was defined as a rise in the mean arterial blood pressure (MABP) of 20 mm Hg or more or a MABP of 105 mm Hg or greater. MABP was calculated by

MABP probably best expresses the impact of any blood pressure on the circulatory hemodynamics. Blood pressure was measured with a mercury sphygmomanometer.

For the first 24 hours, the patients were treated with bed rest, sedatives, and magnesium sulfate, as indicated. The following laboratory tests were done on admission: complete blood count, urinalysis, serum creatinine, blood urea nitrogen, urinary protein, creatinine clearance, prothrombin time, partial thromboplastin time, and platelet count. These tests were repeated after completion of therapy or, in control patients, after 48 hours.

After the first 24 hours of evaluation, the control patients received 5% dextrose in distilled water intravenously: 1,000 ml over 8 hours on the first day, and 500 ml over 4 hours on the second day. The dextran group of patients received 1,000 ml of dextran 40 (Rheomacrodex) over 8 hours during the first day, then 500 ml over 4 hours during the second day. The plasmanate group received 500 ml of plasmanate over 8 hours during the first day, and 250 ml over 4 hours during the second day. Intravenous fluids were administered with a constant-infusion pump. All patients were limited to 40 ml per kilogram per day of intravenous and oral fluids. Diuretics were not used.

Patients were monitored by frequent recordings of

blood pressure, output of urine, and proteinuria, before, during, and after volume expansion therapy. Proteinuria was checked with Multistix\* and analyses of 24-hour urinary protein. These variables were checked by the nurses. Although the nurses were aware of the nature of fluid being infused, there was no suggestion or evidence that this knowledge affected the accuracy of their measurements. Hematocrit and intake and output were checked daily. The "after" readings were recorded on the second day of infusion.

Magnesium sulfate, when indicated, was infused intravenously in the following dose schedule: a loading dose of 4 gm in 100 ml of 5% dextrose solution given over 20 to 30 minutes, followed by 1 gm in 100 ml per hour. The duration of therapy was individualized according to the severity of pre-eclampsia. After completion of volume expansion therapy, further management of the patient depended on the severity of pre-eclampsia and the duration of pregnancy.

### Results

Included in the study were 36 primiparous patients who ranged in age from 15 to 33 years and had pregnancy durations of 28 to 40 weeks. However, three patients were delivered of infants and one withdrew from the study before therapy was completed. This report presents the findings on 32 patients: 13 in the control group, 10 in the dextran group, and nine in the plasmanate group.

The numbers of patients who required magnesium sulfate therapy, who were delivered of infants by cesarean section, and who developed complications in the three study groups are shown in Table I. Indications for cesarean delivery included severe pre-eclampsia, premature twins, and breech presentation. There was one fetal death due to abruptio placentae in the plasmanate group. The fetal gestational age was 32 weeks, and the weight was 1,503 grams. There was one neonatal death due to prematurity in the dextran group. The neonate weighed 936 grams and was at 28 weeks' gestation. About 20% abruptio placentae was discovered at delivery in two other patients: one each in the control and the dextran groups. In both instances, the babies had good Apgar scores.

The effect of infusion of dextran at the rate of 2 ml per minute was similar to that of infusion of plasmanate at the rate of 1 ml per minute for the same period, on the variables studied (Table II). Table III shows the change from before to after volume expansion therapy in the control and the combined plasmanate and dex-

<sup>\*</sup>Ames Company, Division of Miles Laboratories, Inc., Elkhart, Indiana.

Table II. Change from before to after volume expansion therapy in the plasmanate and dextran groups

	Plasmanate $(N=9)$				Dextran (N = 10)			
	Before		After		Before		After	
Variable	. Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
MABP (mm Hg)	107.0	2.3	101.3	2.8	110.0	2.2	102.9	2.7
Urinary protein*	0.7	0.4	0.7	0.3	1.4	0.3	1.1	0.3
Urine output (ml)	1,892	218.8	2,352	142	1,736	205	2,502	263
Hematocrit (%)	35.9	1.0	34.4	1.35	37.9	1.0	35.6	0.9
Creatinine clearance (ml/min)	79.2	11.5	104.7	14.5	62.5	11.1	75.2	15.9

SEM = Standard error of mean.

Table III. Change from before to after volume expansion therapy in the control and the combined plasmanate and dextran groups

	Control (N = 13)				Dextran-plasmanate ( $N = 19$ )				
	Before		After		Before		After `		
Variable	Mean	SEM	1Aean	SEM	Mean	SEM	Mean	SEM	p Value
MABP (mm Hg) Urinary protein* Urine output (ml) Hematocrit (%) Creatinine clearance (ml/min)	107.22 1.00 1,870 34.27 80.70	2.70 0.28 257 2.95 12.34	107.12 1.31 1,564 34.76 87.50	1.96 0.36 172 3.02 12.68	108.62 1.11 1,810 37.00 70.42	1.64 0.29 147 -0.79 8.04	102.18 0.95 2,431 35.06 89.21	1.94 0.22 151 0.81 11.14	p < 0.10 NS† p < 0.01 p < 0.01 NS

SEM = Standard error of mean.

tran groups. The data for all five variables were analyzed via a two-factor analysis of variance (factorstreatment groups and time) with repeated measurements on the same subject, before and after treatment. A specific contrast, namely, the average change in control versus the average change in the combined treatment groups, was tested for significance with an F statistic (two-sided); the p values for this are shown in the table. There was a trend toward lowering of the MABP after volume expansion therapy in the plasmanate-dextran group; but this was significant only at the 10% level. Improvement in output of urine and in hemoconcentration in the plasmanate-dextran group was significant at p < 0.01. The change in urinary protein and creatinine clearance was not significant. No deleterious effects of volume expansion therapy were noted in the patients studied.

### Comment

Normal pregnancy is characterized by a delicate balance between the adrenal glands, placenta, and kidneys. For reasons unknown at present, this homeostasis is disturbed in pre-eclamptic patients. One of the early

pathophysiologic changes in pre-eclampsia is a reduced expansion of blood volume. There is disagreement as to whether this reduced blood volume is the cause or result of the associated hypertension in pre-eclampsia. Goodlin8 and Cloeren and associates5 thought that this reduced blood volume was analogous to chronic shock. However, instead of tachycardia and hypotension, the pulse rate is normal and there is hypertension due to generalized vasoconstriction. Generalized vasoconstriction also affects the function of other vital organs, such as the kidneys, placenta, and liver. Hypertension in preeclampsia appears to be a protective mechanism for the fetus. Attempts to lower the blood pressure in these patients with antihypertensive drugs are likely to have deleterious effects on the fetus and the mother, unless the blood volume is expanded concomitantly.

Blood volume expansion with plasma expanders, such as low-molecular-weight dextran and salt-poor albumin, has been shown to have salutary effects on the pathophysiologic changes of pre-eclampsia.4, 5, 8 Reduced blood volume and high hematocrit are considered to be unfavorable signs in pre-eclampsia. Perinatal survival has been reported to improve when a high

<sup>\*</sup>Urinary protein scale: trace, 0.5; 1+=1; 2+=2; 3+=3.

<sup>\*</sup>Urine protein scale: trace, 0.5; 1+=1; 2+=2; 3+=3.

 $<sup>\</sup>dagger NS = Not significant.$ 

168 Sehgal and Hitt September 15, 1980
Am. J. Obstet. Gynecol.

hematocrit in pre-eclamptic patients was reversed with volume expansion therapy.<sup>4, 8</sup> Goodlin and associates<sup>4</sup> believe that such therapy can reverse the disease process in about 10% of the cases of severe pre-eclampsia; in others, improvement lasts for a variable period of time. Our controlled study shows significant improvement in hemoconcentration and output of urine, and a trend toward lowering of the MABP in patients in whom plasmanate or dextran was used to expand the blood volume.

Benedetti and associates, using a flow-directed pulmonary artery catheter, studied cardiopulmonary hemodynamics in 10 patients with severe pre-eclampsia during labor, delivery, and the early puerperium, and found that the cardiac output was elevated but that the pulmonary artery pressure was not significantly altered in pre-eclamptic compared to normal patients. Also, central venous pressure and pulmonary artery wedge pressure did not correlate in three of the nine patients studied. They suggest that a pulmonary artery catheter be used when fluids are infused into severe pre-eclamptic patients.

It is important to select very carefully the patients who are to be given volume expansion therapy. Patients with heart disease or pulmonary or renal insufficiency either should not be given such therapy, or should be given it under intensive surveillance, since

acute cardiac failure may be precipitated. All patients who are receiving volume expansion therapy require careful surveillance in regard to pulse and respiratory rate, blood pressure, output of urine, and chest auscultation for signs of heart failure.

The increased incidence of abruptio placentae in pre-eclamptic patients is well known. In our series of 32 patients, there was one fetal death associated with complete abruptio placentae; and in two patients, signs of partial abruptio placentae were discovered on delivery of the placenta. In both cases, the newborns had good Appar scores and did well in the nursery.

In selected cases of pre-eclampsia, volume expansion therapy can be an important adjunct to the standard therapy of bed rest, sedatives, magnesium sulfate, and, if necessary, antihypertensive drugs. In preterm patients who respond favorably to this therapy, delivery may be delayed in order to allow the fetus to mature more fully. In term patients, volume expansion therapy before the induction of labor or cesarean section for obstetric reasons can stabilize blood pressure and increase blood volume. Both of these factors may be beneficial to the mother and the fetus during labor and delivery.

We wish to acknowledge the assistance of Dr. John M. Krall in the statistical analysis of the data.

### REFERENCES

- Zuspan, F. P.: Problems encountered in the treatment of pregnancy-induced hypertension, Am. J. Obstet. Gy-NECOL. 131:591, 1978.
- Chesley, L. C.: Disorders of the kidney fluids and electrolytes, in Assali, N. S., editor: Pathophysiology of Gestation, New York, 1972, Academic Press, Inc., vol. 1, p. 437.
- 3. Blekta, M., Hlavaty, V., Trnkova, M., et al.: Volume of whole blood and absolute amount of serum proteins in the early stage of late toxemia of pregnancy, Am. J. Obstet. Gynecol. 105:10, 1970.
- Goodlin, R. C., Cotton, D. B., and Haesslein, H. C.: Severe edema-proteinuria-hypertension gestosis, Am. J. Obstet. Gynecol. 132:595, 1978.
- 5. Cloeren, S. E., Lippert, T. H., and Hinselman, M.:

- Hypovolemia in toxemia of pregnancy: Plasma expander therapy with surveillance of central venous pressure, Arch. Gynecol. **215**:123, 1973.
- Assali, N. S., and Vaughn, D. L.: Blood volume in preeclampsia: Fantasy and reality, Am. J. Obstet. Gynecol. 129:355, 1977.
- 7. Page, E. W.: On the pathogenesis of pre-eclampsia and eclampsia, J. Obstet. Gynaecol. Br. Commonw. 79:883, 1972.
- Goodlin, R. C.: Severe pre-eclampsia: Another great imitator, Am. J. Obstet. Gynecol. 125:747, 1976.
- Benedetti, T. J., Cotton, D. B., Read, J. C., et al.: Hemodynamic observations in severe pre-eclampsia with a flow-directed pulmonary artery catheter, Am. J. Obstet. Gynecol. 136:465, 1980.

### Genetic amniocentesis in twin gestations

SHERMAN ELIAS, M.D.
ALBERT B. GERBIE, M.D.
JOE LEIGH SIMPSON, M.D.
HENRY L. NADLER, M.D.
RUDY E. SABBAGHA, M.D.
ARNOLD SHKOLNIK, M.D.
Chicago, Illinois

Among 1,613 women studied with routire ultrasonography prior to genetic amniocentesis at Northwestern University Medical School, 25 of 26 multiple gestations were detected. Sampling of fluid from both amniotic sacs was requested by 20 women with twin gestations in which both fetuses were ultrasonographically determined to be viable and of normal size. Fluid was obtained successfully from both amniotic sacs in 19 of 20 cases. The conclusions are that (1) twin gestations can be reliably detected by the use of routine ultrasonography, (2) both amniotic sacs can usually be sampled, and (3) the complication rate appears to be minimal to the patient and the fetuses, although the sample size is still small. (AM. J. OBSTET. GYNECOL. 138:169, 1980.)

ANTENATAL diagnosis of genetic disorders is an accepted part of modern obstetric and gynecologic practice. One major problem has been the difficulty of dealing with multiple gestations. Some investigators consider the reliability of detecting twin gestations at 16 to 20 weeks to be low, and further doubt the ability to sample amniotic fluid from both amniotic sacs even if twins are detected. Moreover, the possibility of increased fetal and maternal risks has been raised. As a reflection of such misgivings, many geneticists emphasize that, in the case of twins, diagnostic information may be obtained on only one fetus.1 On the assumption that it is possible to sample only a single amniotic sac in twin gestations, elegant formulas have even been developed to calculate the probability of concordance if the single sampled fluid indicates either a normal or an abnormal fetus.2 In this article, we present our own experience with amniocenteses in twin gestations which indicates that successful sampling of

From the Departments of Obstetrics and Gynecology and Pediatrics, Northwestern University Medicai School.

Presented as an inaugural thesis by Dr. Sherman Elias to the Chicago Gynecologic Society, Chicago, Iilinois, March 21, 1980.

Received for publication April 21, 1980.

Accepted May 19, 1980.

Reprint requests: Sherman Elias, M.D., Section of Human Genetics, Prentice Women's Hospital & Maternity Center, 335 East Superior St., Chicago, Illinois 60611. both amniotic sacs can be accomplished in almost all cases with minimal risks to the patient and the fetuses.

### Material and methods

At Northwestern University Medical School, antenatal genetic studies are usually performed at either of two autonomous genetics units, one located at Children's Memorial Hospital (CMH) (Department of Pediatrics) and the other located at Prentice Women's Hospital and Maternity Center (PWHMC) (Department of Obstetrics and Gynecology). Each genetics program has separate counseling clinics and separate laboratories. However, amniocenteses for both laboratories are performed almost exclusively by three of us (S. E., A. B. G., J. L. S.). The diagnostic program at CMH, directed by H. L. N., was begun in 1968. To date, 1,866 pregnancies have required amniocentesis for genetic studies. Routine grey-scale ultrasonography (A. S.) was introduced in January, 1975; and since then, 1,080 patients have undergone ultrasonographic examination before amniocentesis. Since October, 1979, both greyscale and real-time ultrasonographic monitoring has been used routinely; thus, the last 153 candidates for amniocentesis were studied by both types of ultrasound. Patients who are studied in this program undergo routine ultrasonography at CMH, after which they go by bus or car to PWHMC for amniocentesis. In singleton pregnancies, the amniocentesis is performed without repeating the ultrasonographic studies. In multiple gestations, amniocentesis is performed after further vi-

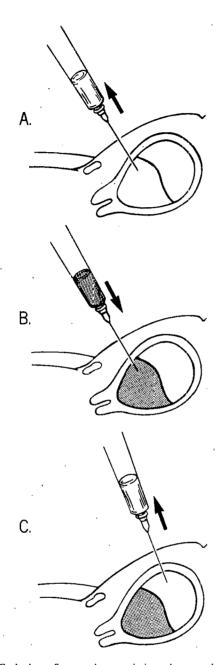


Fig. 1. Technique for amniocentesis in twin gestations, performed immediately after ultrasonographic examination. A, Fluid aspirated from the first amniotic sac. B, Indigo carmine injected into the first amniotic sac. C, Second tap in the ultrasonographically determined location of the second fetus. Clear fluid confirms that the second amniotic sac was successfully aspirated.

sualization in the ultrasonography laboratory at PWHMC (R. E. S.).

A slightly different sequence is followed by the genetics program at PWHMC, where complete prenatal diagnostic services (J. L. S. and S. E.) were first offered in

February, 1977. To date, 533 patients have undergone amniocentesis in this newer program. Routine ultrasonographic monitoring with the use of both grey-scale and real-time ultrasonography has been employed since its inception, and all amniocenteses (singletons and multiple gestations) have been performed in the PWHMC ultrasonography laboratory immediately after scanning.

### Technique for amniocentesis

All amniocenteses in patients with twin gestations are thus performed immediately after scanning in the ultrasonography laboratory at PWHMC. We routinely perform the procedure no earlier than 17 weeks' gestation, one week later than is routine for singleton gestations. Gestational age is estimated on the basis of the last menstrual period, biparietal diameters of the fetuses, and uterine size. Separate amniotic sacs are distinguished by injecting a dye (1 to 3 cc of 0.8% indigo carmine diluted with sterile H2O to give a final concentration of 0.08%) into the sac from which the first sample of fluid (20 cc) is aspirated (Fig. 1). Despite similar colors, indigo carmine has been used rather than methylene blue because the latter has been associated with hemolytic anemia of the neonate, at least when injected into the amniotic sac in the third trimester.3 After ambulation of the patient for 5 minutes, a second amniocentesis is performed in the ultrasonographically determined location of the other fetus. Aspiration of bluish-colored fluid indicates that the first amniotic sac has been reentered. (If twins are monoamniotic, this method would not be applicable; however, monoamniotic twinning is a rare phenomenon.)

### Results

Detection of twins. Among 786 women who underwent amniocentesis prior to the routine use of ultrasonography at CMH, there were two sets of twins (Table I). Neither was detected at the time of amniocentesis (16 weeks' gestation). In both instances, amniotic fluid was inevitably aspirated from only one amniotic sac. Among the 1,080 women who underwent routine ultrasonography, there were 16 (1.4%) with multiple gestations. Only once was a twin gestation not detected, and in this case real-time ultrasonography was not employed. Amniotic fluid was thus aspirated from only one amniotic sac; the products of the pregnancy were two phenotypically normal 24-week fetuses. In the other 15 cases, multiple gestations were detected by ultrasound. Having this information, three patients elected not to undergo amniocentesis, including the only patient with triplets. The two women with

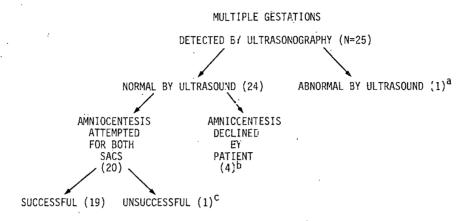


Fig. 2. Genetic amniocentesis in multiple gestations. a, Ultrasonographic studies showed one amniotic sac with oligohydramnios and a severely growth-retarded fetus; the other amniotic sac contained a normal volume of fluid and a normal fetus. Onle the latter amniotic sac was tapped. b, Includes one patient with triplets. c, Patient subsequently was delivered of infants concordant for craniocarpotarsal dysplasia.

Table I. Detection of multiple gestations prior to genetic amniocentesis

	Cases stud	ied prior to routine ultra	sonography	Routinely monitored with ultrasonography			
	No. of cases	No. of multiple gestations	No. detected	No. of cases	No. of multiple gestations	No. detected	
Children's Memorial Hospital	786	.2	0	1,080	· 16*	, 15	
Prentice Women's Hospital and Maternity Center	0	0	. 0	533	10	10	
Totals	786	2	0	1,613	26	25	

<sup>\*</sup>Includes one triplet gestation.

twins were subsequently delivered of normal infants, but the woman who is carrying triplets has still not been delivered. The other 12 women elected to undergo amniocentesis.

Among 533 women who underwent amniocentesis in the prenatal diagnosis program at PWHMC, there were 10 (1.9%) with twin gestations. All 10 cases were detected with ultrasound (Table I). One patient elected not to undergo amniocentesis, and later was delivered of two normal infants. In another case, ultrasonographic studies at 19 weeks showed that one fetus was severely growth retarded (crown-rump length, 6.8 cm) with oligohydramnios, whereas the other fetus was of normal size (biparietal diameter, 4.8 cm) and the volume of amniotic fluid was normal. The couple elected to have only a single tap directed toward the apparently normal sac. Subsequently, the amniotic fluid alphafetoprotein\* was determined to be 1.79 mg percent (borderline elevated for 20 weeks' gestation), and

\*Alpha-fetoprotein assay was performed by Dr. Aubrey Milunsky, Eunice Kennedy Shriver Center, Waltham, Massachusetts.

chromosomal analysis of cultured amniotic fluid fibroblasts revealed a 47,XX,+21 complement. The couple had the pregnancy terminated in another city, where a 47,XX,+21 complement was confirmed in the larger fetus; the growth-retarded fetus showed no obvious malformations, but cytogenetic studies were not performed. The other eight women with twins requested amniocentesis on both sacs (see below).

Success of amniocentesis in twin gestations. From the two genetics programs, 20 sets of twins were thus ascertained in which both fetuses were viable and normal in size, and in which the mother requested sampling from both amniotic sacs (Fig. 2). Using the technique described previously, we successfully obtained fluid from both amniotic sacs in 19 of 20 sets. In a single case, we were unable to enter the second amniotic sac despite two insertions of the needle, and the patient did not wish any further attempts. Studies on the single fluid revealed a 46,XX complement and a normal level of alpha fetoprotein. However, this patient was subsequently delivered at term of one stillborn infant and one liveborn infant. Both infants

172 Elias et al.

September 15, 1980
Am. J. Obstet. Gynecol.

had craniocarpotarsal dysplasia (Freeman-Sheldon syndrome; whistling face syndrome), an autosomal dominant disorder characterized by microstomia and flat midface, talipes equinovarus, and ulnar deviation of the fingers. Our failure to obtain fluid may or may not have been related to the coexisting fetal abnormalities.

In each of the other 19 sets of twins, we successfully obtained fluid from each amniotic sac (Fig. 2). Usually, only two or three insertions of the needle were required per patient. All 19 sets of twins were cytogenetically normal. The twins were both 46,XY in nine sets, both 46,XX in five sets, and discordant for sex (one 46,XX; one 46,XY) in five sets. In the latter, no problems with cell admixture between discordant co-twins was observed, that is, no 46,XX cells were present in cultures of a male fetus whose co-twin was female, and vice versa. The level of alpha-fetoprotein was normal in all cases, albeit with differing values between co-twins. All except one of the 14 sets of twins who have been delivered were normal. In this exceptional set, one twin was normal but the other was stillborn at 40 weeks' gestation with no apparent explanation. One set was delivered prematurely at 28 weeks' gestation, but, other than this, no unusual events were associated with delivery.

### Comment

Our expérience indicates a favorable outlook in regard to (1) ability to detect twin gestations by routine ultrasonography, and (2) ability to obtain information in regard to both fetuses through multiple amniocenteses. Our data contrast with the pessimistic views apparently held by some authors who urge extreme caution and counsel an increased likelihood of failure to sample amniotic fluid from both amniotic sacs. 1 Much of our success in detecting multiple gestations is attributable to recent improvements in ultrasound technology, coupled with increasing investigators' experience. For example, in the 1972-1975 National Institute of Child Health and Human Development collaborative study,5 twins were detected by ultrasonography only one of four times. In our series, routine use of ultrasonography enabled detection of multiple gestations in 25 of 26 (96%) cases. Furthermore, if two viable fetuses and two intact amniotic sacs containing appropriate volumes of fluid are present, each amniotic sac of a twin gestation can be sampled in most cases. In our series, we were successful in 19 of 20 cases in which we attempted to study both fetuses. Both cytogenetic studies and determinations of the level of alpha-fetoprotein have proved to be accurate in all cases. Although our sample size is small, the complication rate appears to be minimal to both the patient and the fetuses.

Our series is among the largest reported thus far for mid-trimester amniocenteses in twin gestations, and it confirms the general success reported by others. Among 1,200 patients studied by Henry and Robinson,7 13 sets of twins were present. Ten of the 13 were detected by ultrasonography. In six of seven patients who elected to undergo amniocentesis, both amniotic sacs were sampled. Thirty-six multiple gestations were encountered by Golbus and associates.8 Prior to the routine use of ultrasonography, 18 twin gestations and two triplet gestations were not diagnosed by the time of amniocentesis, with fluid inevitably obtained from only one amniotic sac; in six additional women, twins w re diagnosed by ultrasonography performed for other reasons. After the introduction of real-time ultrasonography, 10 of 10 twin gestations were detected. Among the total of 15 patients with twin gestations who underwent amniocentesis, both amniotic sacs were successfully tapped in 13 cases. All except one set of twins had normal chromosomal complements; in this set, one of the two fetuses was 47,XX,+21.

The positive experience of our group and several other groups in sampling both amniotic sacs in twin gestations is important because multiple gestation increases with advancing maternal age. The overall twinning frequency is about one in 90 pregnancies. The incidence increases with maternal age up to a peak of one in 65 between ages 35 and 39; thereafter, the rate falls.6 This effect of maternal age is the result of an increased rate of dizygotic twinning, there being very little variation in the monozygotic rates. 6 Since the most frequent indication for antenatal genetic studies is advanced maternal age, it follows that twins will be encountered more frequently in such studies. Of additional concern are data which indicate that among dizygotic twins there is approximately a sixfold increased risk that one or the other twin will be chromosomally abnormal.9 In our series, 1.2% of pregnancies were twin gestations, but there was only one chromosomal abnormality associated with these twins.

If both amniotic sacs are investigated, it is inevitable that in certain cases one will be faced with the dilemma of having one normal fetus and one abnormal fetus. In fact, discordance would be expected more often than concordance. If only one of the twins is abnormal, the couple must be counseled in regard to the potential life expectancy and prognosis for the abnormal fetus; however, the final decision of whether to terminate the pregnancy should be made by the couple. At present, couples should not, in our opinion, be realistically

offered the option of aborting the abnormal but not the normal fetus. Using real-time ultrasonographic guidance, Aberg and associates 10 successfully performed a transabdominal cardiac puncture of a fetus with Hurler's syndrome and avoided abortion of the unaffected co-twin; however, the safety and accuracy of such techniques remain unproved.

### REFERENCES

- 1. Milunsky, A.: Genetic Disorders and the Fetus. Diagnosis, Prevention, and Treatment, New York, 1979, Plenum
- 2. Cox, A. G. W., and Hunter, D. M.: Counseling problems when twins are discovered at genetic amniocentesis, Clin. Genet. 16:34, 1979.
- 3. Kirsch, I. R., and Cohen, H. J.: Heinz body hemolytic anemia from the use of methylene blue in neonates, J. Pediatr. 96:276, 1980.
- 4. Gorlin, R. J., Pindborg, J. J., and Cohen, M. M.: Syndromes of the Head and Neck, ed. 2, New York, 1976,
- McGraw-Hill Book Co., Inc., pp. 216-215.
  5. The National Institute of Child Health and Human Development National Registry for Amniocentesis Study Group: Midtrimester amniocentesis for prenatal diagnosis. Safety and accuracy, J.A.M.A. 236:1471, 1976.

### Discussion

DR. ALLAN G. CHARLES, Chicago, Illinois. Dr. Elias' paper poses interesting moral, technical, and socioeconomic problems. The incidence of twins in the United States is accepted as approximately one in 90 pregnancies. However, there are differences in the various races, with multiple pregnancies occurring most frequently in blacks and least frequently in Orientals. Twinning increases with maternal age, usually because of multiple ovulations, resulting, therefore, in dizygosity. Monozygosity, although difficult to determine, has been reported to vary from as low as 10% in Nigeria to as high as 64% in the Philippines. In the United States, monozygosity occurs in approximately 34% of white and 29% of black twin pregnancies. In a review of 333 twin pregnancies, Farooqui and associates1 reported only two congenital anomalies in 666 infants, an incidence of 0.3%. Petterson and associates,2 in Sweden, reported only 3% congenital anomalies in 1,636 infants of 818 twin pregnancies. Since these large series seem to indicate no significant increase in the incidence of congenital anomalies, and since chromosomal abnormalities represent only a small portion of all congenital anomalies, I would like more information about the incidence of chromosomal abnormalities in twin preg-

Farooqui and associates also observed the disturbing fact that 50% of all twin pregnancies were undiagnosed before delivery, and that only 25% of twin pregnancies were discovered before 32 weeks. In an era of increasing use of ultrasonics for diagnostic purposes in obstetrics, the early diagnosis of twin pregnancies should be made much more frequently. Furthermore, since all amniocenteses should be preceded by ultra-

- 6. MacGillivray, I., Nylander, P. O. S., and Corney, G.: Human Multiple Reproduction, London, 1975, W. B.
- 7. Henry, G., and Robinson, A.: Genetic amniocentesis in twin pregnancies, Am. J. Hum. Genet. 30:53A, 1978.
- 8. Golbus, M. S., Loughman, W. D., Epstein, C. J., Halbasch, G., Stephens, J. D., and Hall, B. D.: Prenatal genetic diagnosis in 3,000 amniocenteses, N. Engl. J. Med. 300:157, 1979.
- 9. Lubs, H. A., and Ruddle, F. H.: Chromosomal abnormalities in the human population: Estimation of rates based on New Haven newborn study, Science 169:495,
- 10. Aberg, A., Mitelman, F., Cantz, M., et al.: Cardiac puncture of fetus with Hurler's disease avoiding abortion of unaffected co-twin, Lancet 2:990, 1978.

sonography, all twin pregnancies should be detected before an amniocentesis is attempted. I was surprised to notice that, in the program at Children's Memorial Hospital, after ultrasonography had been performed there, the patients were sent by bus or car to Prentice Women's Hospital for amniocentesis. Our observation has been that the position of the uterus varies with different degrees of filling of the bladder, hence changing the puncture site for amniocentesis. In our group, amniocentesis is done with the use of real-time ultrasonography to identify the position of the fetus and sac at the time the procedure is performed. I wonder why amniocentesis is done as late as 17 weeks by Dr. Elias' group. At Michael Reese Hospital, there has been no difficulty in culturing cells after 15 weeks' gestation.

Since a significant number of twins may be discordant, and, therefore, genetically or developmentally different, differential amniocentesis can be important for both diagnosis and therapy of discordant twins with differing conditions in utero.

In 1968, using amniography, Bowes and Droegemueller<sup>3</sup> described different degrees of Rh sensitization in a twin pregnancy. Indeed, they attempted, albeit unsuccessfully, twin intrauterine transfusions at different times. In 1975, Bang and associates,4 using a special needle puncture ultrasonic transducer, tapped separate sacs for prenatal karyotyping. In 1977, Picker and associates<sup>5</sup> used ultrasonic guidance to perform differential amniocenteses to assess pulmonary maturity in four sets of twins and in a set of triplets.

In view of the foregoing brief review and Dr. Elias' paper, we know that differential amniocenteses are technically feasible and can be used to gain reliable information about each twin. However, consider the

awful choice faced by the physician and parents should one twin be found to have a chromosomal abnormality. Do you destroy the normal fetus with the abnormal fetus, or preserve the abnormal fetus with the normal fetus? This paper demonstrates the technical feasibility of the double amniocentesis procedure, but barely touches on the difficult bioethical and human issues involved. I will not comment on Aberg and associates' vain attempt at selective abortion via hysterotomy.

### REFERENCES

 Farooqui, M. O., Grossman, J. H., and Shannon, R. A.: A review of twin pregnancies and perinatal mortality, Obstet. Gynecol. Surv. 28:144, 1973.

- 2. Petterson, F., Smedby, B., and Lindmark, G.: Outcome of twin birth. Review of 1,636 children born in twin births, Acta Paediatr. Scand. 64:473, 1976.
- Bowes, W. A., and Droegemueller, W.: Calif. Med. 108: 380, 1968.
- Bang, J., Nielsen, H., and Philip, J.: Prenatal karyotyping of twins by ultrasonically guided amniocentesis, Am. J. OBSTET. GYNECOL. 123:695, 1975.
- Picker, R. H., Smith, D. H., and Saunders, D. M.: A new method of amniocentesis using ultrasonography in multiple pregnancy to assess the second twin, Obstet. Gynecol. 50:489, 1977.

### Copyright information

The appearance of a code at the bottom of the first page of an original article in this JOURNAL indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc., 21 Congress St., Salem, Mass. 01970, (617)744-3350, for copying beyond that permitted by Section 107 or 108 of the U. S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale. For reprint quantities of 50 or more, please contact Publisher.

### A simplified intrapartum numerical scoring system

### The prediction of high risk in labor

IAN MORRISON, M.B., CH.B., F.R.C.S.(C.)
LORRAINE CARTER, R.N
SHARILYN McNAMARA, R.N.
MARY CHEANG, M.MATH.
Winnipeg, Manitoba, Canada

An analysis of 1,994 consecutive parturient women showed that 472 (23%) could be assigned to a high-risk category on the basis of an intrapartum score of  $\geq$ 3. Perinatal mortality, neonatal morbidity, and the rate for operative intervention were all significantly greater for the high-risk group (p < 0.0001). Of the total population, 11% were designated to be at high risk by combining intrapartum and antepartum scores, and 71% of this group had an abnormal intrapartum outcome (p < 0.0001). For this study, 63% of the patients with an abnormal outcome for labor were admitted to the labor floor for 6 hours or longer, and this is an indirect measurement of the potential that exists for optional management. The 'imitations of intrapartum scoring systems are discussed, particularly with respect to their design, the prediction of preventable deaths, and the category of hospital for which they might prove most useful. (AM. J. Obstet. Gynecol. 138:175, 1980.)

SEVERAL STUDIES have demonstrated that numerical systems of risk scoring in pregnancy can be used to predict the liklihood of perinatal death.<sup>1-5</sup> Some authors have restricted the use of such systems to the antepartum period, whereas others have included an intrapartum risk score and shown that this, in conjunction with an antepartum component, increases the predictive accuracy of the scoring system.<sup>1, 3, 4</sup> The ultimate practical application of these numerical scoring systems would be their implementation on a regional basis to screen and identify those pregnancies that have a significantly greater statistical risk of perinatal death; in this manner these high-risk pregnancies could receive further investigation and appropriate management at specific centers if the risk to the fetus is

From the Departments of Obstetrics and Gynecology and Computer Sciences, University of Manitoba.

This study was supported by a grant from St. Boniface General Hospital Research Foundation, Inc.

Received for publication February 27, 1980.

Revised April 29, 1980.

Accepted May 12, 1980.

Reprint requests: Ian Morrison, M.D., Department of Obstetrics and Gynecology, St. Boniface General Hospital, 409 Tache Ave., Winnipeg, Manitoba, Canada R2H 2A6. confirmed. The use of scoring systems for this purpose in community and regional hospitals requires the use of reasonably objective clinical findings that are sufficiently prospective in nature to allow changes in the management of the patient or transfer of the mother; in the interests of time and compliance, the list of factors to be scored should not be exhaustive or excessively complex.

It has already been shown that such modification and simplification of an existing antepartum scoring system can still fulfill the original function without an appreciable loss of accuracy.5 However, it has not been demonstrated that similar adaptation of intrapartum systems can be successful. Also, it has been argued that the use of intrapartum factors as a screening device to identify the fetus at risk does not allow sufficient time to institute corrective or preventive measures to alter outcome. Furthermore, the possibility of predicting events other than mortality and morbidity-such as operative intervention-has not been reported. For these reasons, a prospective evaluation of a simplified intrapartum system of risk scoring was carried out in one of the tertiary centers in Winnipeg, and the intrapartum factors were selected to complement the antepartum scoring system already in use in the province of Manitoba.5, 6

Table I. Intrapartum factors

Labor	Score
Labor ≥20 hours	2
Slow latent phase progress—<3 cm dilatation with contractions for 10 hours	1
Slow active phase progress—"no progress" or <1.5 cm dilatation in 2 hours	2
Meconium in first stage—dark, fresh, or heavy	4
Meconium in first stage—light, old staining	1
Associated conditions	
Gestation <34 weeks	3
Premature rupture of membranes ≥24 hrs	2
Syntocinon induction or augmentation of labor	2
Miscellaneous	
Height: <5 feet 2 inches (155 centimeters)	1
Weight: <100 pounds (45 kilograms)	1
≥200 pounds (90 kilograms)	
Smoking (current): ≥20 to 25 cigarettes per day	1
Ethnic: North American Indian	î

The purpose of this study was to test the accuracy of a simplified intrapartum scoring system to predict the outcome of labor defined by three measurements: perinatal mortality, perinatal morbidity, and maternal morbidity defined by the occurrence of primary cesarean sections or midforceps Kielland rotations. The secondary objective was twofold: to evaluate the potential use of this intrapartum system in conjunction with the simplified antepartum scoring form already used in this region since 1977, and to assess the interval of time that might be available for alternate management once the patient was discovered to be at risk.

### Material and methods

The study population consisted of 1,999 consecutive parturient women who were admitted to the labor unit of St. Boniface General Hospital over a 9-month period. This hospital, one of two tertiary centers in Winnipeg, has a 34% high-risk component identified by antepartum risk scoring of 2,760 deliveries for 1978, and is a University teaching hospital. All patients who were in labor, or in whom induction or delivery was planned, were admitted prospectively to the study. Two experienced nurses who were familiar with the collection of data and the interpretation of perinatal events completed the intrapartum scoring form; and because the results obtained for each patient were not released to the attending physician, the management of the patient was not influenced by the risk score.

The twelve factors incorporated in the form represent information that might be obtained, or events that might occur, sufficiently early in the first stage of labor to allow a *choice* of intervention (Table I). Because the antepartum scoring system used on a regional basis already contained items with respect to multiple preg-

nancy, malpresentation, or breech, these factors were not repeated in this intrapartum system. Each inrapartum factor was assigned a numerical value based upon, and approximately proportional to, the inrapartum scoring system reported by Hobel and associates.3 Whereas events in the second stage, such as shoulder dystocia, forceps delivery, general anesthesia, and emergency situations, such as a prolapsed cord, will all affect fetal outcome and have been included in other intrapartum scoring systems, these events predude alternative choices of management or maternal transfer from a smaller hospital and were omitted from this form. Similarly, conditions associated with significant antepartum hemorrhage were deliberately excluded from the design of this scoring system on the basis that maternal transfer is hazardous in these emergency situations because of the geographic distances that exist between hospitals in our region.

Abnormalities incompatible with life were considered to be an extraneous cause of mortality unrelated to intrapartum events, and at the conclusion of the study, but prior to analysis, an independent retrospective review of the neonatal deaths was carried out by the neonatologist to exclude those cases in which congenital abnormalities were the predominant or major cause of death. For the purposes of the study, perinatal deaths were defined as intrapartum stillbirths or neonatal deaths, with birth weights of 500 grams or greater; antepartum stillbirths that occurred prior to admission to the labor floor were excluded. Morbidity was defined for surviving newborns by an Apgar score of 6 or less, at 1 or 5 minutes, or admission to the intensive-care nursery. Neonatal deaths were excluded from these figures for morbidity. Maternal morbidity was defined by the occurrence of primary cesarean sections or midcavity Kielland forceps rotations.

The information from this study was coded for computer analysis, and the total numerical score for each patient was determined by adding the assigned values that were present for each factor. An arbitrary division between a low-risk and a high-risk score was chosen on the basis of statistically significant differences for each of the three outcomes of labor that were selected for the study. This value was then accepted as the criterion for placing patients in a low-risk or high-risk group during labor and for subsequent comparisons. From the previous study by Coopland and associates,5 an antepartum risk score of ≥3 had already been shown to indicate a high-risk pregnancy. Statistical tests of significance included the chi-square and Student's t test; discriminant analysis was performed retrospectively once the results of the study were known.

**Table II.** Prediction of mortality and neonatal and maternal morbidity with intrapartum score of ≥3

		Perinatal mortality†		Neonatal* morbidity†		Maternal morbidity†	
Intrapartum score	Total deliveries	No.	Rate	No.	Rate (%)	No.	Rate (%)
0-2 ≥3	1,522 472	2 14	1.3/1,000 29.6/1,000	218 144	14.3 30.5	192 184	12.6 38.9

<sup>\*</sup>Excludes neonatal deaths.

### Results

One thousand nine hundred and ninety-nine patients were delivered of 2,004 babies, with 25 deaths, for a perinatal mortality rate of 12.4/1,000. There were no intrapartum stillbirths. Operative intervention, in the form of primary cesarean sections (13.8%) and midforceps rotations (5%), occurred in 18.8% of the series and was considered to be representative of intrapartum maternal morbidity. Eight percent of the neonates weighed less than 2,500 grams, and one third of these were less than 34 weeks' gestation. The cesarean section rate for the group of infants who weighed <2,500 grams was 14%, and 30% of these low-birthweight babies who were delivered by cesarean section had an Apgar score of less than 7 at 5 minutes. There were five neonatal deaths due to congenital abnormalities incompatible with life, and the mothers who were delivered of these babies were excluded from the study for the reasons already described. The analysis was then based upon the remaining 1,994 patients and their risk scores.

Table II summarizes these results for perinatal mortality, morbidity, and maternal operative intervention, with a numerical score of 3 selected as the division between a low-risk and high-risk intrapartum outcome. Because each mother was scored only once, mortality associated with multiple births was registered as a single death in order to avoid bias in favor of the risk scoring system. These deaths included twins and one set of triplets, and all were associated with risk scores greater than 3. Hence, of the 20 deaths that remained after the exclusion of congenital abnormalities, only 16 are shown in Table II. Had each death been counted individually, it would have increased the perinatal mortality rate for the group scoring ≥3. Of the 1,994 deliveries, 472 were high-risk, representing 23% of the total, and these deliveries were responsible for 14 of the 16 perinatal deaths. The predictive value of this score for each measurement of outcome for the 472 patients who scored ≥3 is indicated by perinatal mortality rate of 29.6/1,000, a morbidity rate of 30.5% (double that of the low-risk group), and a rate for op-

**Table III.** Distribution of deaths by birth weight

<1,500 grams	1,500 to 2,500 grams	>2,500 grams
9 + (4*)	5	2

<sup>\*</sup>Deaths associated with multiple pregnancies.

erative intervention of 38.9% (increased threefold compared to that for the low-risk group). These predictive values derive their significance by comparison with the corresponding predictions for the patients assigned to the low-risk category. There were 342 events, consisting of mortality, neonatal morbidity, and maternal morbidity, that occurred in the 472 high-risk patients, for a predictive value of 72%; conversely, in the low-risk category, a normal outcome was correctly predicted for 73% of events. The incorrect prediction of outcome, particularly neonatal and maternal morbidity, for 27% of the low-risk cases may reflect the design of the scoring system which excluded specific intrapartum events.

The distribution of deaths by birth weight is shown in Table III. All neonates with a birth weight of less than 2,500 grams who died had intrapartum scores of  $\geq$ 3; there were only two deaths among infants who weighed more than 2,500 grams, and both occurred in the low-risk category. This distribution by weight category is of some significance in the interpretation of the results and will be discussed later.

Table IV shows the distribution of patients with the dual systems of risk scoring that combine an intrapartum score with an antepartum risk score; for both systems a score of ≥3 denoted high-risk. The cases were subdivided on the basis of various combinations of low-risk and high-risk shown in the table. Of 1,994 patients, there were 221 (11%) who scored high-risk with both intrapartum and antepartum systems, and within this group of 221 patients, 71% had an abnormal intrapartum outcome. The predictive accuracy of this combination of high/high-risk was significantly greater than that of any of the other combinations examined singly or together. It should be

tp = < 0.0001.

Table IV. Prediction of abnormal outcome for labor with intrapartum and antepartum systems of risk scoring

Scorin	ng system	Qu	tcome		
Antepartum score	Intrapartum score	Abnormal* (n = 634)	Normal $(n = 1,360)$	Total $(n = 1,994)$	% Abnormal
(1) <3 (low) (2) ≥3 (high) (3) <3 (low) (4) ≥3 (high)	<3 (low) <3 (low) ≥3 (high) ≥3 (high)	183 177 116 158	839 323 135 63	1,022 500 251 221	18 35 46 71

<sup>(4)</sup> Compared to (1), (2), (3): p = <0.0001. (3) Compared to (2): p = <0.01.

Table V. Duration of admission to labor unit

Time	Total series	Abnormal outcome
≤2 hours	507 25%	23% 146
3 to 5 hours	408 21%	14% 87
6 to 20 hours	913 46%	52% 329
>20 hours	166 8%	11% 72
·	1.994 100%	100% 634

Table VI. Ranking of intrapartum factors

Intrapartum factors	Rank by discriminant analysis	Rank by frequency in series (totallabnormal)
Gestation <34 wk	. 1	12 10
Arrest	. 2	4 3
Meconium (fresh)	3	5 6
Height	· . 4	2 2
Latent stage	. 5	8 4
Premature rupture of membranes >24 hr	6	11 12
Meconium (old)	7	. 10 11 -
Induction	8	1 1

stressed that in contrast to Table II, which contained each intrapartum event even when more than one event occurred in the same patient, Table IV is restricted to the actual patient count regardless of the number of occurrences; this offers a more realistic interpretation for the clinician. Despite the use of both systems of risk scoring, 183 of the 634 patients with an abnormal outcome for labor (28%) were assigned to the low/low-risk category, and therefore these patients with an abnormal outcome were not predicted by the combination of scoring systems. Moreover, neither of the deaths of neonates with birth weights greater than 2,500 grams were predicted by either system (Table III). Of the 16 neonatal deaths, 14 were predicted by the intrapartum score and 12 by the antepartum score.

In Table V, arbitrary intervals of time have been selected to divide the series into four groups on the basis of the duration of admission to the labor unit, and

these time intervals are shown for the total population and for those patients with an abnormal outcome. For the total series, there was very little difference between the duration of labor and the duration of admission to the labor floor. The more accurate and practical measurement for the management of the individual patient is the duration of admission; it is this measurement that indicates the potential for alternate choices of management or maternal transfer, on the assumption that risk scoring is performed soon after admission. The table shows that 63% of the patients (401) with an abnormal outcome for labor were admitted for 6 hours or longer.

Discriminant analysis was used for the three measurements of outcome to discover the significant variables based on linear discriminant function; Table VI shows that only eight of the 12 factors originally chosen for the intrapartum risk score contributed significantly to the results. The predictive accuracy of the intrapartum scoring system was retested with these reduced factors and showed no loss of accuracy. Similarly, the contributions of the antepartum risk score and its "intrapartum" component, with respect to malpresentation and multiple pregnancy, were separately tested and discovered to correlate significantly with outcome. In fact, compared to the intrapartum factors used in this study, these antepartum components ranked in importance second only to prematurity, secondary arrest of labor, and the presence of fresh meconium. Table VI lists, in descending rank, the eight intrapartum factors that were found to be significantly associated with outcome after discriminant analysis. In the same table, for comparison, these factors are ranked by the frequency of their occurrence. Discriminant analysis ranked a gestation of less than 34 weeks as the most significant variable associated with an abnormal outcome. However, a gestation of less than 34 weeks ranked only twelfth and tenth in frequency, respectively, for the series and for those with an abnormal outcome. Similarly, induction ranked lowest in

<sup>\*</sup>Cases associated with neonatal mortality or morbidity, or maternal morbidity.

its association with an abnormal outcome, but occurred most frequently for the series. From the comparison of the ranking of the intrapartum factors for the total series and the abnormal group (Table VI), it can be inferred that the differences in outcome were not significantly related to differences between these two populations. It is interesting to note that, although 13% of the patients in our population smoked 20 or more cigarettes per day at the time of their admission to the labor floor, this variable was not significantly associated with a poor outcome for labor.

# Comment

The purpose of this study was to test a simplified intrapartum numerical system of risk scoring. The results show that, on the basis of a numerical score of  $\geq 3$ , patients can be assigned to low-risk or high-risk categories that have a relationship to the outcome of labor. Several studies have already shown that intrapartum scoring can predict the likelihood of perinatal mortality and morbidity, but these systems have been quite extensive and have contained factors related to the second stage of labor or its prolongation, such as shoulder dystocia, outlet forceps, or a second stage of more than 21/2 hours. Other studies have included intrapartum emergencies, such as prolapsed cord, abruptio placentae, and problems of anesthesia. These conditions undoubtedly affect fetal outcome, but would occur as late events or as emergency situations which would preclude a choice of management or maternal transfer; too short a time interval between the occurrence of an intrapartum event and the delivery means that the management of the patient must be predicated on the immediate circumstances at the hospital of admission. In this study, we wished to know whether selected events limited to the first stage of labor would offer a reliable degree of prediction about the outcome and yet allow enough time for changes in management, consultation, or transfer of the patient, if this proved to be necessary. In contrast to antepartum events, the progress of labor allows less time for the assessment of the patient, and if an intrapartum scoring system is to have some practical value, it should have the potential to alter fetal outcome and yet retain its predictive capacity. This is particularly relevant to the current emphasis on regionalization, which is an attempt to select the most appropriate facility for the confinement of the individual patient. For this study, 63% of the patients with an abnormal outcome for labor were admitted to the labor floor for 6 hours or longer, and this is an indirect measurement of the potential that exists for optional management. On the other hand, an admission interval of 2 hours or less must be considered to

preclude elective management, and 23% of the patients with an abnormal outcome were in this category. It is difficult to judge whether an initial assessment and effective changes would be possible for the remaining 14% of patients who were admitted for 3 to 5 hours, but it would seem to be a reasonable assumption that some of these patients would be candidates for transfer. Therefore, more than half of the patients assigned to a high-risk category in our population have the potential for reassessment and possible transfer after risk

However, in addition to this aspect, it is equally important that an intrapartum system demonstrate its predictive accuracy for the outcome of labor. In this series, patients who were assigned to a high-risk category had a significantly greater perinatal mortality rate than those who scored <3. Of the 1,994 patients, 23% were classified as high-risk, and the majority of perinatal deaths occurred in this group. However, the distribution of deaths by birth weight as seen in Table III shows that more than 50% of the neonates who died weighed less than 1,500 grams. It is generally accepted that the deaths of neonates who weigh 1,500 grams or more are potentially preventable,7 and in this series there were only seven such deaths that could be placed in this category. Furthermore, two of these deaths, both in infants who weighed more than 2,500 grams, were assigned to the low-risk category. In other words, in this study, only five of 18 deaths identified by risk scoring were potentially preventable (27%). Since the risk scoring factors did not identify the two deaths of infants who weighed more than 2,500 grams, and since there were no intrapartum stillbirths, the significant correlation between risk score and neonatal mortality was due to the high proportion of deaths in low-birth-weight infants in the study; this tendency is confirmed by the results of the discriminant analysis, which showed prematurity to have a highly significant association with outcome, despite its infrequent occurrence in the total series. Therefore, despite the significant statistical result in this study, the predictive value of this or any other intrapartum scoring system must be judged from the pragmatic viewpoint of potentially preventable deaths; there is no point to the prediction of inevitable deaths and the unnecessary transfer of patients. That this system does have some practical merit is indicated by its ability to screen an obstetric population and restrict the high-risk category to 23%; also five of the seven potentially preventable deaths did occur within this category. In addition, a high-risk score was significantly associated with morbidity, particularly operative intervention, which would suggest that the factors listed in the risk form have the potential to identify the

180 Morrison et al. September 15, 1980
Am. J. Obstet. Gynecol.

risk of mortality in the mature infant. It is worth noticing that the two deaths for the weight category greater than 2,500 grams were due to circumstances that would not have been discovered by clinical risk scoring. One death was the result of prematurity in an infant who was delivered by elective cesarean section, and the other occurred in an infant of an undiagnosed gestational diabetic patient. There is merit to the suggestion of Aubrey and Pennington<sup>1</sup> that clinical risk systems should be complemented by ancillary prenatal laboratory investigations. The distribution of deaths in this series with a high proportion in the low-birth-weight category reflects the nature of the obstetric practice in this high-risk referral unit, and one would anticipate that in this situation intrapartum stillbirths and neonatal deaths among infants with weights of ≥2,500 grams should be minimal. Nevertheless, with this skewed distribution, the validity of the results of any intrapartum scoring system tested in a referral center must remain conjectural if applied to the smaller hospital; it is our opinion that this question can be answered only through the use of risk scoring on a regional basis.

Other authors have indicated that the combined use of antepartum and intrapartum risk scores increases the accuracy of prediction, and we would agree with this statement.3 The antepartum risk form that is used in this region has been previously reported on,5,6 and in this study, 11% of our total population was designated high-risk by both antepartum and intrapartum scores, with 71% of this identified group having an abnormal intrapartum outcome. These results confirm that the best results will be achieved with dual risk scoring, and that an antepartum score has a significant role in the identification of intrapartum risk and outcome. However, with retrospective analysis it is evident that the combined use of both risk scores fails to identify 28% of all the patients with an abnormal outcome; this lack of sensitivity confirms the unpredictable nature of obstetric events and limits the function of risk scoring to a screening process. The sensitivity of risk scoring can be increased, but only by decreasing the efficiency

of its screening capacity with the identification of increasingly larger numbers of patients.

The number of factors contained within this intrapartum scoring form can be reduced from 12 to eight, because discriminant analysis showed that four of the factors were not significantly related to outcome. These factors were: labor of ≥20 hours, prepregnancy weight, smoking, and ethnic origin. If these factors were discarded, it would allow the substitution of other factors that might prove to be more significantly related to maternal and fetal outcome or that were more appropriate for a particular region and its local circumstances. Again, we would caution that the lack of significance for these factors in this series is related to the particular circumstances pertaining to the practice at this hospital; for example, labors of ≥20 hours might prove to be significantly related to poor fetal outcome for hospitals that lack the equipment for fetal monitoring.

This study has demonstrated some of the inherent difficulties in the interpretation of an intrapartum scoring system for the prediction of fetal outcome. It is difficult, if not artificial, to consider intrapartum events in isolation separate from their closely related and antecedent antepartum factors. It has been stressed that the practical value of any system is limited to the prediction of potentially preventable deaths, and intrapartum systems should be designed for a specific function, with a view to the different needs of a teachng center compared to a community hospital. In contrast to antepartum risk scoring, intrapartum assessnent by the numerical assignment of high-risk has not, To our knowledge, been tested in regional or community hospitals. Until this event occurs, the practical "alue of this abbreviated system remains to be proved in this situation. The circumstances and events related to labor will almost certainly mean that many intrapartum problems must continue to be managed in the hospital which initially admits the patient, and that any hospital involved in obstetric care must be prepared to cope with these events.

# REFERENCES

- Aubrey, R. H., and Pennington, J. C.: Identification and evaluation of high-risk pregnancy: The perinatal concept, Clin. Obstet. Gynecol. 16:3, 1973.
- 2. Goodwin, J. W., Dunne, J. T., and Thomas, B. W.: Antepartum identification of the fetus at risk, Can. Med. Assoc. J. 101:57, 1969.
- 3. Hobel, C. J., Hyvarinen, M. A., Okada, D. M., et al.: Prenatal and intrapartum high-risk screening, Am. J. Obstet. Gynecol. 117:1, 1973.
- 4. Sokol, R. J., Rosen, M. G., Stojkov, J., et al.: Clinical appli-
- cation of high-risk scoring on an obstetric service, Am. J. OBSTET. GYNECOL. 128:652, 1977.
- Coopland, A. T., Peddle, L. J., Baskett, T. F., et al.: A simplified antepartum high-risk pregnancy scoring form, Can. Med. Assoc. J. 116:999, 1977.
- 6. Morrison, I., and Olsen, J.: Perinatal mortality and antepartum risk scoring, Obstet. Gynecol. 53:362, 1979.
- Usher, R.: Changing mortality rates with perinatal intensive care and regionalization, Semin. Perinatol. 1:309, 1977.

# Electrocardiographic changes induced by suction curettage for elective termination of pregnancy

LEE M. MABEE, JR., M.D.
BRUCE E. DUNN, M.D.
C. WILLIS SHERRER, M.D., F.A.C.O.G.
Honolulu, Hawaii

To determine if significant electrocardicgraphic changes occur during suction curettage for elective termination of pregnancy, continuous electrocardiogram tracings were obtained from 103 patients prior to, during, and after suction curettage. Sixty-eight of 103 patients (66%) demonstrated transient sinus tachycardia presumably attributable to pain (P < 0.001). Eleven of 103 patients (10.6%) demonstrated premature atrial contractions or premature ventricular contractions during suction curettage (P < 0.005). When more rigid (8 or 9 mm) curets were used, a threefold increased incidence of extrasystoles was noted. In a comparison of the incidence of electrocardiographic changes in parous versus nulliparous patients, no statistically significant differences could be demonstrated. (Unlike in previous published reports on intrauterine manipulation, bradycardia was not noted.) (AM. J. OBSTET. GYNECOL. 138:181, 1980.)

BRADYCARDIA, tachycardia, tachycardia-arrhythmia, syncope, and seizures have been reported with intrauterine manipulation. Taubin, in 1932, reported that 27 of 3,600 patients undergoing uterotubal insufflation felt faint, and seven patients lost consciousness. Marshak and associates reported three cases of shock secondary to hysterosalpingography. Ringrose reported five grand mal seizures associated with 2,000 intrauterine contraceptive device (IUD) insertions, and one in 20 patients experienced faintness. Sobrerof stated that 10% of nulliparous women receiving a rigid IUD would experience syncope.

Acker and associates,<sup>5</sup> in 1973, reported on 87 patients undergoing IUD insertions. Thirteen percent demonstrated bradycardia or arrhythmia, and 12% demonstrated tachycardia during the procedure. In a

From the Departments of Obstetrics and Gynecology and Cardiology, Tripler Army Medical Center.

Presented at a meeting of the Armed Forces District, American College of Obstetrics and Gynecology, Washington, D. C., October 17, 1978.

The views expressed herein are those of the authors and de not necessarily reflect the views of the United States Army or the Department of Defense.

Received for publication January 14, 1980.

Revised April 29, 1980.

Accepted May 29, 1980.

Reprint requests: Captain Lee M. Mabce, Jr., MC, Department of Obstetrics and Gynecology, Ft. Leavenworth, Kansas 66048.

series of 25 patients undergoing IUD insertion reported by Sherrod and Nicholl,<sup>6</sup> 32% demonstrated bradycardia and 25% developed tachycardia. They reported almost identical electrocardiographic changes with uterine sounding. Aznar and associates,<sup>7</sup> in 1976, reported a series of 204 IUD insertions, with 46 patients demonstrating tachycardia and 53 developing bradycardia (Table I).

Faintness, syncope, and nausea have been reported with gynecologic procedures, including uterine sounding and dilatation of the cervix. However, electrocardiographic tracings were not obtained to document any changes.<sup>1, 2</sup>

In view of the above reports, the present study was undertaken to determine if electrocardiographic changes occurred during elective termination of pregnancy by suction curettage.

# Methods

One hundred three normal women were selected at random for the present study. Seventy-five were dependent wives; 28 were on active duty in the armed forces. The age distribution was 16 to 45 years (mean 24.4). There were 39 nulliparous and 64 parous patients. Twenty-six patients had undergone a previous elective termination of pregnancy.

Preoperative evaluation included a history, physical examination, and routine laboratory evaluation consisting of complete blood count, six-parameter sequential multiple analyzer test, serologic test for syphilis, urine

Study	Procedure	Sinus tackycardia	Sinus bradycardia	Total No. of patients
Acker et al., <sup>5</sup> 1973	IUD insertion	10 (12%)	11 (13%)	
		8 (9%) throughout	(Bradycardia/arrhythmia)	87
Sherrod and Nicholl, <sup>6</sup> 1976	IUD insertion	5 (25%)	8 (32%)	25
,	Uterine sounding	4 (16%)	8 (32%)	25
Aznar et al.,7 1976	Hysterometer	1	1	. 7
•	IÚD insertion	46 (25%)	53 (26%)	204
	Endometrial biopsy	7 (25%)	6 (21%)	28

Table I. Electrocardiographic changes reported with intrauterine manipulation

analysis, and blood type and Rh determination. Eight patients were referred to the Department of Cardiology for evaluation, with a history of either rheumatic heart disease or a cardiac murmur. Two patients were found to have significant heart disease. The first had a history of rheumatic heart disease since childhood and was found to have significant mitral stenosis and aortic insufficiency. The second had significant pulmonary valvular insufficiency. Both patients received subacute bacterial endocarditis prophylaxis. The remaining six patients evaluated were found to have innocuous flow murmurs.

The patients were placed in the dorsal lithotomy position prior to any testing and remained recumbent on the operating table for at least 5 minutes upon termination of the procedure.

Prior to the procedure, a baseline 1-minute electrocardiogram strip was obtained, with either Lead II or Lead V<sub>1</sub>. The patient was then continuously monitored via electrocardiographic strip during administration of intravenous medication and throughout the procedure. Vital sign measurements were obtained prior to, during, and upon termination of the procedure. In the recovery area, vital signs were monitored every 15 minutes for 1 hour.

All patients received a combination of 25 mg of Phenergan (promethazine) intravenously, 50 mg of Demerol (meperidine) intravenously, and 5 to 10 mg of Valium (diazepam) intravenously, titrated slowly for sedation. A uterosacral block with 100 mg of Xylocaine was employed as well.

Twenty-one patients underwent preoperative dilatation of the cervix with laminaria. Laminaria were left in place for 8 to 12 hours to effect dilatation. The remaining 82 patients underwent mechanical dilatation of the cervix.

Depending on the estimation of gestational age, a flexible 6 mm Berkeley vacuum curet (for a mean gestational age of 8.2 weeks) or a rigid 8 or 9 mm Berkeley vacuum curet (for a mean gestational age of 9.9 weeks) was used. A Berkeley vacuum source was employed in all cases. Chi-square analysis was employed to test statistical significance of the results.

### Results

Initial electrocardiograms revealed the following abnormalities. Five patients demonstrated sinus tachycardia prior to any manipulation. In these patients, the mean heart rate was 103 bpm (range 100 to 110) prior to the procedure and 114 bpm (range 110 to 130) during the procedure. One patient with an isolated premature atrial contraction prior to the procedure had sinus tachycardia during the procedure. After intravenous medication was given, one of the above five patients developed a normal sinus rhythm of 90 bpm without further change during the procedure.

After injection of intravenous analgesics (Phenergan, Valium, Demerol), no electrocardiographic changes except as above were noted.

Following dilatation of the cervix either by mechanical means or previously by laminaria, the following electrocardiographic changes were noted during suction curettage. Sixty-eight of 103 patients (66%) demonstrated transient sinus tachycardia during the procedure, the heart rate increased 43% (mean 80 bpm prior and 114 bpm during). Sinus tachycardia was noted in 31 of 39 nulliparous patients and in 37 of 64 parous patients. Sinus bradycardia was not noted (Table II).

Patients described various degrees of discomfort with the procedure. However, all were able to tolerate the procedure. No syncopal episodes or hypotensive changes were noted.

Berkeley Vacurettes were used in all cases. A flexible 6 mm curet was employed in 75 cases. A rigid 8 or 9 mm curet was employed in 28 cases. A threefold increased incidence of extrasystoles was noted when the more rigid curet were employed (Table III). When a fexible curet was employed, 6.7% of patients demonstrated extrasystoles as compared with 21.4% of patients when the more rigid curet was employed.

The effect of mechanical dilatation of the cervix was compared to that of prior dilatation of the cervix with laminaria, and no statistically significant differences could be demonstrated (Table IV).

Eleven of 103 patients (10.6%) demonstrated atrial or ventricular premature contractions during the suction

Table II. Electrocardiographic changes noted in relationship to parity

		,			
	Elec				
Parity	Sinus tachy- cardia	Sinus brady- cardia	Prema- ture con- traction	N <sub>0</sub> change	No. of cases
Nulli - parous	31 (79%)	0	2 (5%) (1/2*)	7	39
Parous	37 (58%)	0	9 (14%) (5/9*)	23	64
Total	68†	0	11‡	30	103

<sup>\*</sup>Six of 11 demonstrated both tachycardia and extrasystoles. †P < 0.001.

**Table III.** Flexibility of curet compared to electrocardiographic changes

	Elec				
Flexibility of curet	Sinus tachy- cardia	Sinus brady- cardia	Premature beats	No change	No. of.
Flexible	47 (63%)	0	5 (6.7%) (1/5*)	24	75
Rigid	21 (75%)	0	6 (21%) (5/6*)	6	28
Total	68	0	11'	30	103

<sup>\*</sup>Six of 11 demonstrated both tachycardia and extrasystoles.

curettage (P < 0.005). Alexander and associates8 reported finding premature ventricular beats in 4.2% of all electrocardiograms obtained on all outpatients at the Lahey Clinic in 1967. Patients demonstrating extrasystoles during suction curettage are shown in Table V.

# Comment

Investigators have reported electrocardiographic changes (predominantly bradycardia) associated with intrauterine manipulation.5, 6 Bradycardia, tachycardia, arrhythmias, and syncope have all been reported with IUD insertions, endometrial biopsy, and intrauterine manipulation.5-7

Sherrod and Nicholl<sup>6</sup> reported bradycardia with insertion of a rigid IUD. Acker and associates<sup>5</sup> reported that 13% of patients undergoing IUD insertion demonstrated bradycardia and arrhythmia. Aznar and associates<sup>7</sup> reported bradycardia in 47% of patients undergoing insertion of a rigid IUD. They also reported that a positive correlation of rigid IUDs and nulliparous patients associated with an increased incidence of electrocardiographic changes. In our study, bradycardia was not noted nor was an explanation readily available for its absence.

Table IV. Method of dilatation of cervix compared to electrographic changes

,	Electrocardiographic changes							
Method of dilatation	Sinus tachy- cardia	Sinus brady- cardia	Prema- ture con- traction	No change	No. of cases			
Laminaria	16 (76%)	0	4 (14%)	4	21			
Mechanical dilatation	52 (63%)	0	(3/4*) 7 (8.5%) (3/7*)	26	82			
Total	68	0	11	30	103			

<sup>\*</sup>Six of 11 demonstrated both tachycardia and extrasystoles.

Table V. Patients demonstrating abnormal electrocardiograms: Premature contractions

Case No.	Curet size (mm)	Parity	Electrocardio- gram prior to procedure	Electrosardiogram during procedure
1	6	P	NSR	Occasional PACs
2	6	P	NSR	One PVC
3	6	P	NSR	One PVC, late diastole
4	6	N	NSR	Two PACs/11 unifocal
	•			fixed PVCs
5	6	P	ST 110	One PVC, tachycardia
6	9	P	NSR	One PVC, late
				diastole, tachycardia
. 7	9	P	NSR	One PVC, tachycardia
8	9	P	NSR	Two unifocal PVCs
9	9	P	NSR	One PAC, tachycardia
10	9	N	NSR	One PAC, tachycardia
11	9	P	NSR	Two unifocal PVCs,
				tachycardia

N = Nulliparous. P = Parous. NSR = Normal sinus rhythm. PAC = Premature atrial contraction. PVC = Premature ventricular contraction.

Most patients in this study developed sinus tachycardia during or prior to the procedure presumably secondary to catecholamine release attendant to anxiety and pain. Scherf and associates9 have shown that vagotonia may, in certain individuals, facilitate the emergence of ectopic beats. However, the lack of bradycardia in our study does not support increased vagal tone. Presumably the minimal arrhythmias produced are related to a sympathetic induced increased excitability. Since these electrocardiographic charges were episodic and asymptomatic, antiarrythmic drug therapy was not indicated.10

# Conclusion

We could find no previously documented series of electrocardiographic monitoring during uterine evacuation. Our study differs from previously published reports on electrocardiographic changes secondary to uterine manipulation in that bradycardia, syncope, and

P < 0.005.

seizures were not noted. Sinus tachycardia was the most commonly noted electrocardiographic change, occurring in 66% of cases. No statistically significant differences could be demonstrated between the nulliparous and parous patients. Eleven of 103 patients (10.6%) demonstrated either premature atrial or premature ventricular contractions during curettage.

Syncope was not noted, presumably because the pa-

tients remained in the dorsal lithotomy position. Although electrocardiographic changes were noted, none of the patients was symptomatic. Two patients with known heart disease tolerated the procedure without difficulty and did not demonstrate electrocardiographic changes. No treatment was required for the above echocardiographic abnormalities.

### REFERENCES

- Rubin, I. C.: Twelve year's experience with uterotubal insufflation; diagnostic and therapeutic, Am. J. Obstet. Gynecol. 24:561, 1932.
- 2. Marshak, R. H., Poole, C. S., and Goldberger, M. A.: Hysterography and hysterosalpingography, Surg. Gynecol. Obstet. **91**:182, 1950.
- Ringrose, C. A. D.: Intrauterine contraceptive devices, J. Reprod. Med. 6:96, 1971.
- Sobrero, A. J.: Intrauterine devices in clinical practice, Fam. Plann. Perspect. 3:16, 1971.
- Acker, D., Boehm, F. H., Askew, D. E., and Rothman, H.: Electrocardiographic changes with intrauterine contraceptive device insertion, Am. J. Obstet. Gynecol. 115:458, 1973.
- 6. Sherrod, D. B., and Nicholl, W.: Electrocardiographic

- changes during intrauterine contraceptive device insertion, Am. J. Obstet. Gynecol. 119:1044, 1974.
- Aznar, R., Reynoso, L., Ley, E., Gamez, R., and DeLeon, M.: Electrocardiographic changes induced by insertion of an intrauterine device and other uterine manipulations, Fertil. Steril. 27:92, 1976.
- 8. Alexander, S., DeSai, D. C., and Hershberg, P. I.: Clinical significance of ventricular premature beats in an outpatient population, Am. J. Cardiol. 29:250, 1972.
- Scherf, D., Cohen, J., and Rafailzadeh, M.: Excitory effects of carotid sinus pressure, enhancement of impulse formation and of impulse condition, Am. J. Cardiol. 17:240, 1966.
- Jelinek, M. V., Lohrbauer, L., and Lown, B.: Antiarrhythmic drug therapy for sporadic ventricular ectopic arrythmias, Circulation 49:659, 1974.

# Red cell exchange in the pregnancy complicated by a major hemoglobinopathy

MARIE M. KEELING, M.D.
J. PATRICK LAVERY, M.D.
ANITA U. CLEMONS
ROBERT L. SCHAEFER
PATRICIA D. BLANDFORD
ESTUS A. HARRIS
Louisville, Kentucky

A new method of partial erythrocyte exchange for pregnancies complicated by a major hemoglobinopathy is described. The Haemonetics 30 Cell Separator allows efficient withdrawal and discard of the patient's erythrocytes. The patient's leukocytes, platelets, and plasma are conserved and returned with washed, compatible donor red cells which contain Hb AA. Three pregnant black women with significant hemoglobinopathies were treated by this modality during their pregnancies. Vaginal term deliveries were accomplished in each case. The method offers advantages in the efficiency of blood quantity displacement, patient comfort, adaptability to the patient with severe anemia, and the use of outpatient facilities. The method is suggested for use whenever a patient with an obstetrically significant hemoglobin variant needs transfusions of erythrocytes. (Am. J. Obstet. Gynecol. 138:185, 1980.)

HEMOGLOBIN variants which cause problems in obstetric patients are sickle cell anemia (Hb SS) and the closely related disorders of Hb SC and Hb S-beta thalassemia.<sup>1</sup>

Previously, when blood exchange was used in patients with these disorders, it had been accomplished by a manual "push-pull" technique. Originally, whole bank blood was substituted for that removed by phlebotomy. Recently, various refinements of that method have been tried, especially the use of buffy-coat-poor, washed erythrocytes. This procedure involves, however, a considerable and undesirable loss of the patient's own leukocytes, platelets, and plasma.

Using a Haemonetics 30 Cell Separator, we have developed an efficient method of red cell exchange in which only the patient's erythrocytes are discarded.

From the Norton-Children's Hospitals Blood Bank, and the Departments of Obstetrics and Gynecology and Pathology, University of Louisville School of Medicine. Received for publication March 27, 1989.

Accepted April 21, 1980.

Reprint requests: Dr. Marie M. Keeling, Blood Bank, Norton-Children's Hospitals, Inc., 200 East Chestnut St., Louisville, Kentucky 40202. Compatible, washed red cells which contain Hb AA are the major replacement blood product.

Three black women were treated with red cell exchange during the late second and third trimesters of pregnancy. Their labors were uncomplicated. Vaginal delivery of healthy term infants resulted in all cases. There was no significant postpartum morbidity in any patient.

# Material and methods

Hematologic evaluation was by standard methods. The complete hemoglobin profile, derived from hemolysates of freshly drawn anticoagulated whole blood, included cellulose acetate electrophoresis at pH 8.4 and citrate agar electrophoresis at pH 6.0 (Helena); determination of fetal hemoglobin; ferrohemoglobin solubility; heat stability; diethylaminoethyl cellulose (DE 52) microcolumn chromatographic determination of Hb A<sub>2</sub>; and quantitation of all hemoglobin variants by DE-52 microcolumn chromatography. A complete profile was performed before and after each exchange. Additionally, after each "pass," the major hemoglobin moieties were determined by microcolumn chromatography. In this way, an accurate estimate of the efficiency of exchange was possible. Donor bloods were

186 Keeling et al.

September 15, 1980
Am. J. Obstet. Gynecol.

Table I. Change in hemoglobin level and concentrations of Hb A before and after exchange transfusion
with Haemonetics 30 Cell Separator in 3 patients with hemoglobinopathies

	Gestational age Passes with		Hemoglobin		% Hb A	
Patient ·	Gestational age (wk)	Haemonetics 30	Preexchange	Postexchange	. Preexchange	Postexchange
M. C. (Hb SC)	24	5	12.4	11.1	. 0	34
, ,	33	7	10.7	11.1	14	59
	40	6 .	12.8	12.9	-32	60
B. B.* (Hb SC)	37	6	11.3	12.3	0	65
, ,	40	0	12.3		49	
A. P. (Hb SS)	25	12	8.1	12.1	0	68

<sup>\*</sup>Patient B. B. received only one exchange, and the laboratory value at delivery is indicated at the 40-week point.

subjected to alkaline pH electrophoresis (Helena) to ascertain the presence of Hb AA. Cord bloods were evaluated by cation column chromatography. Blood banking procedures, involving donor and recipient, were performed by conventional techniques. Estimation of blood volume was by nomogram.\*

Patients received standard antepartum care; spontaneous labor was allowed and the mode of delivery was governed by the usual criteria. Apgar scores and gestational age were assessed by a staff neonatologist.

The Haemonetics Model 30 (Haemonetics Corporation, Braintree, Massachusetts) was used for the red blood cell (RBC) exchange. The patient's blood was separated into packed red blood cells (PRBCs) and buffy-coat plasma fractions with each cycle or "pass" on the machine. The PRBCs were removed and replaced with an equal volume of freshly washed red blood cells (WRBCs) which contained Hb AA. The patient's buffy-coat plasma fraction was reinfused. Sufficient "passes" were performed to remove and replace a volume of PRBCs equal to that of the patient's original estimated RBC volume. During each exchange, only fresh (less than 3 days' old) WRBCs were used. The patient's extracorporeal volume was never allowed to exceed 15% of the total blood volume.

The software arrangement on the Model 30 was the same as that employed in a routine plateletpheresis. Acid citrate dextrose Formula B (Fenwal) was the anticoagulant. The regular adult bowl, 225 ml, was used on two patients; the 100-ml pediatric bowl was required for the third patient because of her small red cell volume. By means of the standard double venipuncture technique, all replacement WRBCs were infused into the "drawing" arm, and the buffy-coat plasma fractions were reinfused into the "return" arm.

A typical "pass" was performed as follows: When the 225-ml bowl was used, blood was drawn at a rate of 40 to 60 milliliters per minute. As the bowl filled with

blood, the air was displaced into the air plasma bag. When plasma flowed past the platelet three-way clamp, it was diverted into a 600-ml transfer bag attached to the platelet port. When the buffy coat was approximately 1 cm from the hub of the bowl, the drawing rate was slowed to 20 ml/min. Collection was terminated 90 seconds after the effluent line turned pink with RBCs. The patient's RBCs were pumped up to the reinfusion bag. The bag was weighed after each pass. A 2,000-ml transfer pack was connected to the reinfusion bag; erythrocytes were allowed to drain by gravity into the transfer pack, which was later discarded. After the first pass, a visual plasma hemoglobin was performed. An equal volume of donor WRBCs was infused into the patient's "drawing" arm immediately. The buffy-coat plasma fraction was detached from the platelet port and reinfused into the "return" vein. A typical exchange took from 4 to 6 hours, depending on the size of the bowl used and the number of passes required.

In addition to the special hemoglobin-oriented studies, routine pre-pheresis laboratory evaluation consisted of complete blood count (CBC), platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, serum calcium, creatinine, blood urea nitrogen (BUN), total protein, albumin, and blood culture. At the end of the procedure, all studies, except creatinine, BUN, albumin, and total protein, were repeated.

# Results

Three patients with significant hemoglobin variants were treated by the above-described method during the course of their pregnancies. Two of these patients had hemoglobin Hb SC, and the third had hemoglobin Hb SS. One patient, M. C., had a history of significant and frequent crises which required multiple hospitalizations. She underwent three exchange transfusions during the course of her pregnancy, one being performed at the time of an impending crisis.

The second patient, B. B., was similarly affected with

<sup>\*</sup>Data and references are available on request.

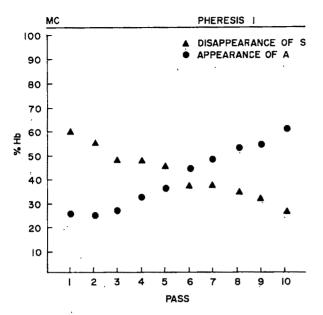


Fig. 1. Serial change of HB A and S during pheresis II in patient M. C.

hemoglobin SC disease. Although she had suffered no significant complications in the past, an exchange transfusion was performed electively prior to delivery. After the exchange, the patient had a significant sense of well-being and greater activity tolerance.

The third patient, A. P., had Hb SS. She had required multiple hospitalizations for her disease. With these frequent crises, many of which were due to severe anemia, prophylactic transfusions had been given. She underwent a twelve-unit exchange at 25 weeks' gestation. This was well tolerated. She did not return to our facility for subsequent care, but rather was treated by intermittent transfusions for the remaining portion of her pregnancy. The outcome of all these pregnancies was spontaneous labors with term infants appropriate for gestational age and no significant maternal morbidity. Table I illustrates the time in gestation and the number of exchange passes that were performed and the preexchange and postexchange hemoglobin profiles.

# Comment

Pregnancy in women with major hemoglobinopathies, such as Hb SS, SC, and S-B thalassemia, has become more common within the past two decades. Increased understanding of the pathophysiologic features of these disorders and better general management have resulted in the survival of these patients beyond puberty. However, perinatal mortality rates in such gestations are still in the range of 17% to 33%.1, 2

Maternal problems are also significant. Rates of

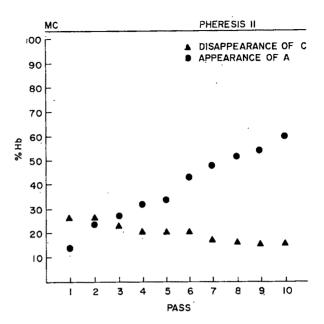


Fig. 2. Serial change of HB A and C during pheresis II in patient M. C.

pregnancy-induced hypertension which approached 25% and significant infectious disease problems, such as pneumonia, infections of the urinary tract, and postpartum endometritis, contribute to morbidity in patients with such hemoglobinopathies.3

In one institution, sickle cell anemia and SC disease were the third most common cause of maternal mortality, barely being exceeded by toxemia and infection.<sup>2</sup>

Especially hazardous is the pregnancy in which the mother harbors Hb SC. Maternal morbidity is intense, with life-threatening pulmonary and neurological problems as the chief complications. Indeed, maternal deaths are not unusual in this group.2, 4

The technique of partial exchange transfusion for such obstetric cases was first employed in 1963, and its use was advocated in 1968,5 with subsequent reports confirming its efficacy.3

The largest series which involved partial exchange transfusion showed a decrease in maternal morbidity and improved perinatal outcome.3 The investigators delivered approximately four units of buffy-coat-poor, washed red cells to the mother, with the goal of achieving a level of 40% Hb A in the maternal circulation. The perinatal mortality was 3%, which demonstrated a significant improvement over the previously reported 34% for such a high-risk population in the same institution. The rate of prematurity and low-birth-weight infants also declined.6

Manual methods of partial red cell exchange appear to offer advantages over previous conservative therapy. Hyperviscosity with the sequelae of sickling-associated microinfarctions is avoided by maintaining Hb A above 30%.<sup>7</sup>

The present method easily maintained the level of 30% Hb A in both Hb SC patients (Table I). More importantly, it was readily sustained in one patient (M. C.) for 4 months by two additional exchanges and one two-unit transfusion of washed red cells. The other patient (B. B.) had only a short follow-up in which her pre-pheresis level of 0% Hb A rose to 65% after pheresis, and was 49% 3 weeks later.

Maintenance of circulating concentrations of Hb A above 30% virtually converts a major hemoglobinopathy to the status of sickle trait (Hb AS). In patients with Hb AS, pregnancy is unassociated with any unusual morbidity, apart from an increase in infections of the urinary tract.

It is interesting to note that a previously reported difficulty was that of increasing the Hb A levels above 40% by means of the push-pull techniques in patients with Hb SC, regardless of the amount of blood exchanged.<sup>8</sup>

In both cases of Hb SC disease, Hb S was displaced with relative ease by Hb A, whereas Hb C was removed with difficulty. Figs. 1 and 2 depict this perplexing situation, for which no explanation can be offered at this time.

With the exception of the exchange performed on the severely anemic patient with sickle cell disease, no attempt was made at hypertransfusion. The patient's red cell mass was brought up only to the pretransfusion level.

We believe that this technique obviates two undesirable side effects of previous methods. First, raising the total circulating blood volume by simple transfusion might readily result in circulatory overload in a patient already compromised by pregnancy. Secondly, increasing the red cell mass to a higher level in order to correct an "anemia" to achieve an arbitrary "normal" adds unnecessary erythrocytes, the destruction of which adds to the preexisting iron overload which can be found in such patients.

The present technique offers several advantages in the relative efficiency of blood displacement. It is adaptable to the severely anemic individual by means of the pediatric bowl; withdrawal of only unwanted erythrocytes from the patient is accomplished, with return of his/her leukocytes, platelets, and plasma; and the option of outpatient therapy is available.

The question of the value of prophylactic exchange transfusion in gestations complicated by a major hemoglobinopathy remains unsettled. To those many obstetricians who consider it a part of optimal therapy, the method has obvious worth.

In conclusion, whenever the transfusion of erythrocytes is indicated in a patient with a hemoglobinopathy, whether it be a sickling disorder, thalassemia, or an unstable variant, this method might be considered to be the one of choice in a referral center.

# REFERENCES

- Pritchard, J. A., Scott, D. E., Whalley, P. J., et al.: The effects of maternal sickle cell hemoglobinopathies and sickle cell trait on reproductive performance, Am. J. Obstet. Gynecol. 117:662, 1973.
- Fort, A. T., Morrison, J. C., Berreras, L., et al.: Counseling the patient with sickle cell disease about reproduction: Pregnancy outcome does not justify the maternal risk, Am. J. Obstet. Gynecol. 111:324, 1971.
- 3. Morrison, J. C., and Wiser, W. L.: The use of prophylactic partial exchange transfusion in pregnancies associated with sickle cell hemoglobinopathies, Obstet. Gynecol. 48: 516, 1976.
- Davey, R. J., Esposito, D. J., and Jacobson, R. J.: Partial exchange transfusion as treatment for hemoglobin SC disease in pregnancy, Arch. Intern. Med. 138:937, 1978.

- Ricks, P.: Further experience with exchange transfusion in sickle cell anemia and pregnancy, Am. J. Obstet. Gy-NECOL. 100:1087, 1968.
- 6. Morrison, J. C., and Wiser, W. L.: The effect of maternal partial exchange transfusion on the infants of patients with sickle cell anemia, J. Pediatr. 89:286, 1976.
- Anderson, R., Cassell, M., Mullinax, G. L., et al.: Effect of normal cells on viscosity of sickle cell blood, Arch. Intern. Med. 111:286, 1963.
- 8. Morrison, J. C., Whybrew, M. D., and Bucovaz, E. T.: Use of partial exchange transfusion preoperatively in patients with sickle cell hemoglobinopathies, Am. J. Obstet. Gynecol. 132:59, 1978.
- 9. Editorial: Transfusion therapy in pregnant sickle cell disease patients, Am. J. Obstet. Gynecol. 134:851, 1979.

# Isoelectric heterogeneity of human chorionic gonadotropin: Presence of choriocarcinoma specific components

KATSUMI YAZAKI, M.D.
CHIAKI YAZAKI, M.D.
KATSUMI WAKABAYASHI, Ph.D.\*
MASAO IGARASHI, M.D.
Maebashi, Japan

Comparative clinical studies were carried out on the isoelectric heterogeneity of serum human chorionic gonadotropin (hCG) in normal pregnancy and trophoblastic disease by means of isoelectric focusing and radioimmunoassay. The immunoreactive hCG components in sera of women with normal pregnancy were composed of seven peaks with isoelectric points of 3.9, 4.1, 4.4, 4.7, 5.0, 5.8, and around 6.7. These same components were also observed in the sera of patients with hydatidiform mole and invasive mole. However, in the sera of patients with choriocarcinoma, three additional components with isoelectric points of 3.2, 3.5, and 3.7 were observed in considerable amounts. The presence of those three specific components suggests the possibility to develop a new diagnostic procedure for the detection of choriocarcinoma. (AM. J. OBSTET. GYNECOL. 138:189, 1980.)

SINCE THE ADVENT of isoelectric focusing (IEF), isoelectric heterogeneity has been shown to be a very common property of glycoprotein hormones.<sup>1</sup>

Isoelectric microheterogeneity of purified hCG was reported by several investigators, who examined polyacrylamide gel, etc.<sup>2-5</sup> Following an examination of the electrical nature of his hCG preparation by IEF, van Hell<sup>6</sup> reported that at least eight zones were distinguishable with isoelectric points (pIs) from pH 3.8 to 5.9.

In an earlier investigation, the molecular size and charge of human chorionic gonadotropin (hCG) from normal pregnancy were shown to be different from

From the Department of Obstetrics and Gynecology, School of Medicine, Gunma University.

Supported by Ford Foundation Research Grant 740-0405:

Received for publication February 20, 1980.

Revised April 17, 1980.

Accepted May 29, 1980.

Reprint requests: Dr. Katsumi Yazaki, Department of Obstetrics and Gynecology, School of Medicine, Gunma University, Syowamachi, Maebashi, 371, Japan.

\*Present address: Hormone Assay Center, Institute of Endocrinology, Gunma University, Maebashi, 371, Japan. those of hCG from molar pregnancy. The molecular size of molar hCG was shown to be greater than that of normal pregnancy. These facts indicate the heterogeneity or polymorphism of hCG. Moreover, the different physicochemical properties may be of clinical value for specific diagnosis of trophoblastic disease.

The previous reports on the isoelectric heterogeneity of hCG were observed with purified preparations of hCG.<sup>2-7</sup> The purpose of this investigation was to elucidate by IEF the pattern of hCG in untreated serum from patients with normal pregnancy, molar pregnancy, and choriocarcinoma.

In this report the IEF patterns of immunoreactive (IR) hCG in normal pregnancy and trophoblastic disease are compared.

# Material and methods

Serum samples. Samples of 1 ml of blood were obtained from 10 healthy pregnant women between the sixth and thirty-eighth week of pregnancy, from seven patients with intact hydatidiform mole, from four patients with intact destructive mole, and from four patients with choriocarcinoma before chemotherapy. The diagnosis of trophoblastic neoplasia in all patients was confirmed by histopathologic examination.

The blood was clotted at 4° C and centrifuged. The

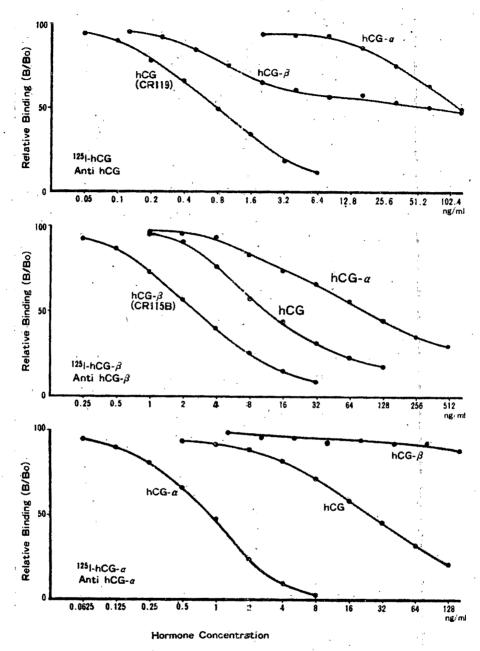


Fig. 1. Cross-reaction in homologous hCG, hCG- $\alpha$ , and hCG- $\beta$  RIA systems.

serum was separated and stored at  $-30^{\circ}$  C until the analysis by focusing.

**IEF.** A preparative IEF column, size 25 ml, prepared in our laboratory, was used.<sup>8</sup> As carrier ampholytes, Ampholines, pH 2.5 to 4, pH 3.5 to 10, pH 4 to 6, and pH 5 to 7 (LKB Produkter), were mixed at volumes of 5:2:8:5, respectively, for a total concentration of 2.8%, to make up a linear pH gradient from 2.5 to 7.0. For the stabilization of the IEF solution, a sorbitol density gradient of 5% to 50% was used. Then 100  $\mu$ l of serum sample was added to the IEF solution. A small

amount of acetylated cytochrome c (pI 3.9) was added to the solution as a reference marker. IEF was performed with the anode at the bottom of the column. The average time for focusing was 90 to 96 hours at 2 to 4° C. During this time, the voltage applied was increased stepwise from 300 to 900 V. After focusing, the solution was eluted at a flow rate of  $100 \,\mu$ l/min and 65 fractions of  $450 \,\mu$ l were collected. The pH of the eluate was measured simultaneously during the collection with a special automatic device. Each fraction was vortexed and  $100 \,\mu$ l of the fraction was diluted to 1:10

with gel-phosphate-buffered saline (PBS, consisting of 0.01M sodium phosphate, 0.14M sodium chloride, 0.01% merthiolate, and 0.1% gelatin, pH 7.5) and stored at -30° C until assay for hCG.

Radioimmunoassay (RIA). The homologous hCG,  $hCG-\alpha$  subunit, and  $hCG-\beta$  subunit RIAs were carried out by the double-antibody method with the National Institute of Health RIA kits. hCG (CR119) and hCG- $\alpha$  and hCG- $\beta$  (CR115B) were labeled with <sup>125</sup>I by the chloramine-T method according to Greenwood and associates9 with minor modification. The assay system consisted of 400 µl of gel-PBS, 200 µl of standard or sample solution in gel-PBS, 100 µl of diluted antiserum (anti-hCG, 1:100,000; anti-hCG-α, 1:20,000; anti-hCG-\beta, 1:50,000) in PBS containing 0.05M ethylenediaminetetra-acetate and 1% normal rabbit serum, and 100 µl of the labeled hormone solution in gel-PBS. The 1st incubation was carried out at 4° C for 48 hours. Then 200  $\mu$ l of a diluted goat anti-rabbit gamma globulin serum, H-4, prepared in our laboratory, was added as the second antibody and incubated at 4° C for 48 hours. Results were expressed as nanograms of the preparations used for radioiodination.

# Results

RIA. The relative specificity of the assay systems to hCG, hCG- $\beta$ , and hCG- $\alpha$  is shown in Fig. 1. With the native hCG assay system, the cross-reaction with hCG-β was about 15%. The cross-reaction of hCG-α was negligible. For the hCG- $\beta$  assay system, the cross-reaction with hCG was about 20% and that with hCG-α was about 3%. The hCG-α assay system had low crossreaction with hCG of about 3% and negligible crossreaction with hCG-β.

# IEF patterns.

hCG preparations. The patterns of IR hCG, IR hCG- $\alpha$ , and IR hCG-β, supplied by the NIH as pure preparations, are shown in Fig. 2, a, b, and c. A purified preparation of hCG (CR119) was resolved into several components, five of them appearing at pH 3.9, 4.1, 4.4, 4.7. and 5.0 (Fig. 2, a) and a few components appeared as a large neutral to basic peak at pH above 5.8.

The purified preparation of hCG-β (CR115B) had four distinct components between pH 3.9 and 4.5 with some minor components between pH 5.0 and 6.8. There was a large acidic peak below pH 3.0 (Fig. 2, b).

The purified preparation of hCG- $\alpha$  migrated as a neutral or basic component (Fig. 2, c).

hCG in sera.

NORMAL PREGNANCY. A typical IEF pattern of IR hCG in serum of a normal pregnant woman (7 weeks of pregnancy) is shown in Fig. 3. These components were tentatively designated for convenience as components

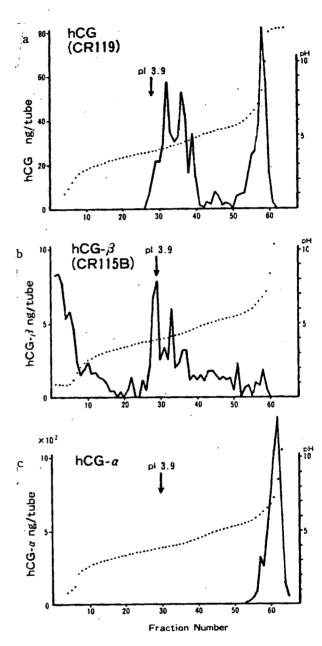


Fig. 2. IEF pattern of three hCG preparations. Dots in the figure represent the pHs of the fractions. The arrows in the figure show the fraction where the pI marker (acetylated cytochrome c, pI 3.9) was eluted.

A (pI 3.9), B (pI 4.1), C (pI 4.4), D (pI 4.7), E (pI 5.0), F (pI 5.8), and G (approximately pI 6.7). In general, the relative amounts of components B and C were large, while those of A, D, E, F, and G were small.

HYDATIDIFORM MOLE. A typical IEF pattern of hCG in serum of a patient with intact hydatidiform mole is shown in Fig. 4. The pIs of the components of serum hCG in hydatidiform mole were identical to those in normal pregnancy, e.g., the seven components A, B, C, D, E, F, and G were present.

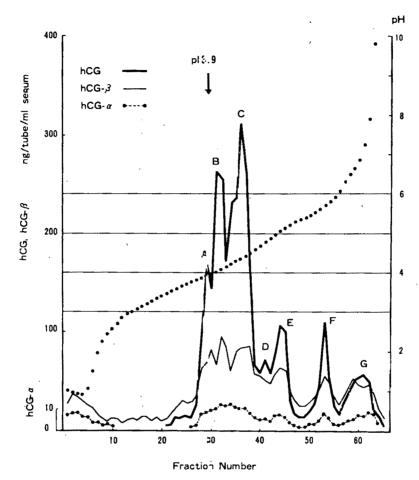


Fig. 3. IEF pattern of serum hCG in normal pregnancy (seventh week). Dots in the figure represent the pHs of the fractions. The arrow in the figure shows the fraction where the pI marker (acetylated cytochrome c, pI 3.9) was eluted.

Peaks B and C always appeared as major components, while the amount of D was variable among the patients.

Invasive mole. A typical IEF pattern of hCG in the serum of a patient with intact invasive mole is shown in Fig. 5. The seven common components observed in normal pregnancy and hydatidiform mole were also recognized in this case. The amounts of components A and D varied among the patients.

CHORIOCARCINOMA. Two typical IEF patterns of IR hCG in the sera of two patients with choriocarcinoma are shown in Figs. 6 and 7.

The seven components found in normal pregnancy were also observed. However, in choriocarcinoma, component A, which was always a minor component in normal pregnancy, became a major component in all four cases. Moreover, three additional components were observed at pH 3.7, 3.5, and 3.2 and were immunoreactive with anti-hCG and anti-hCG- $\beta$ . They were tentatively designated as  $T_1$ ,  $T_2$ , and  $T_3$ , respectively.

Components  $T_1$ ,  $T_2$ , and  $T_3$  were all significantly elevated (P < 0.001) from the baseline levels at comparable pHs of patterns of hCG from the sera of patients with normal pregnancy and hydatidiform mole.

# Comment

The present investigation was carried out with the aim of finding an isoelectric property of IR hCG of different origin, namely, normal placenta and trophoblastic tumors. The analyses of the isoelectric property of hCG in serum should be clinically useful in diagnosis and for treatment of hCG-producing tumors.

The pIs of IR hCG components found by the present IEF analysis in untreated sera of normal pregnant women agreed well with those in previous reports in which purified hCG from urine was used. For example, van Hell<sup>6</sup> reported that at least eight zones with isoionic points from pH 3.8 to 5.9 could be distinguished. In our present data, there were at least six IR hCG components with pIs from 3.9 to 5.8 and the same compo-

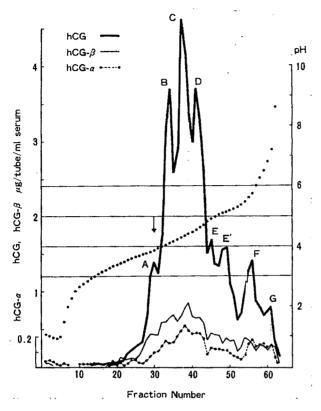


Fig. 4. IEF pattern of serum hCG in hydatidiform mole. Dots in the figure represent pH of the fractions. The arrow in the figure shows the fraction where the pI marker (acetylated cytochrome c, pI 3.9) was eluted.

nents were also observed in CR119, placental extract, and urine of normal pregnancy. Although in firsttrimester pregnancy component G was a major component in the placenta and urine, it was a minor component in serum and was not further resolved because of the poor resolution power in this pH area.

Merz and associates<sup>5</sup> separated purified hCG into six fractions with pIs ranging from pH 4.0 to 5.2. The most biologically active fraction was reported to have an isoelectric point of pH 4.2. The pIs of five of six fractions corresponded well to those of our components A, B, C, D, and E. This corresponds well to our own data which showed that the most biologically potent component was B (pI = 4.1) when bioassayed by testosterone synthesis with rat Leydig cells. Chan and associates<sup>7</sup> also reported that the pIs of molar hCG ranged from 3.5 to 5 by IEF. In our data, IEF patterns of IR hCG in molar pregnancy were almost the same as those in normal pregnancy and contained the main common components with pIs from 3.9 to 5.0. Components F and G were larger in second-trimester pregnancy than in the first and third trimesters, and their content was small in the sera of all patients with tropho-

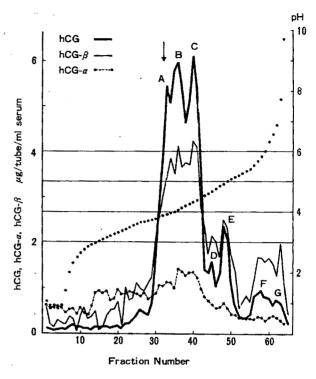


Fig. 5. IEF pattern of serum hCG in invasive mole. Dots in the figure represent the pHs of the fractions. The arrow in the figure shows the fraction where the pI marker (acetylated cytochrome c, pI 3.9) was eluted.

blastic disease. IEF patterns of hCG in sera of all four patients with choriocarcinoma were very similar, and components T1, T2, and T3 were distinguished in considerable amounts (T1, 12%; T2, 7%; T3, 2%).

In the management of trophoblastic disease, the early detection of choriocarcinoma is very important, whether or not morphologic or radiologic diagnosis is obtained. The assay of T1, T2 and T3 will be useful for this purpose.

After the administration of combination chemotherapy (methotrexate, actinomycin D, Endoxana), components T1, T2, and T3 became larger than other components in the serum of a patient who responded well to chemotherapy, but the IEF pattern of hCG did not change in the sera of a patient who did not respond to the same combination chemotherapy. We cannot form definite conclusions from only two cases, but the IEF pattern of hCG in serum may be correlated to responsiveness to chemotherapy.

Although our present analytical method required rather a long time, a further simplified method can be put to practical use for clinical examination. These results suggest the possibility that detection and quantitation of these specific components (T1, T2, T3) would constitute a new diagnostic procedure for choriocar-

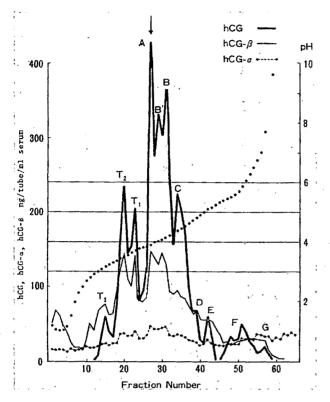


Fig. 6. IEF pattern of serum hCG in choriocarcinoma. Dots in the figure represent the pHs of the fractions. The arrow in the figure shows the fraction where the pI marker (acetylated cytochrome c, pI 3.9) was eluted.

cinoma, but further research may be required to confirm this.

We wish to express our gratitude to Dr. R. E. Canfield, College of Physicians and Surgeons of Columbia University, New York, New York, for supplying

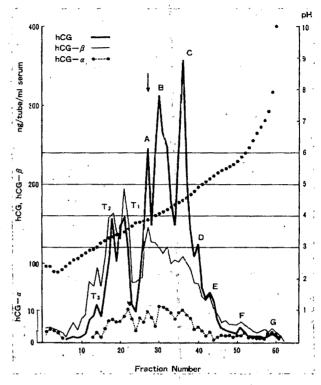


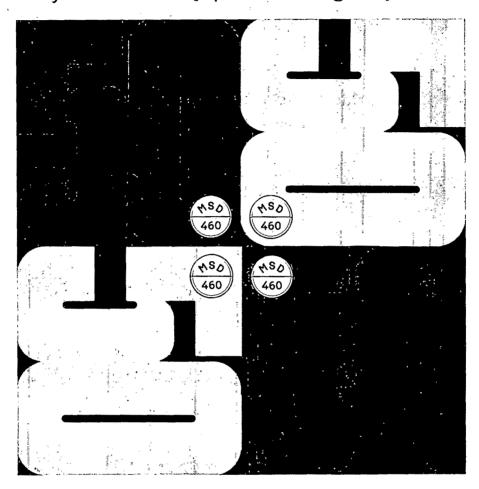
Fig. 7. IEF pattern of serum hCG in choriocarcinoma. Dots in the figure represent the pHs of the fractions. The arrow in the figure shows the fraction where the pI marker (acetylated cytochrome c, pI 3.9) was eluted.

the hCG preparations and to the National Institute of Arthritis, Metabolism, and Digestive Diseases and the National Institute of Child Health and Human Development, NIH, Baltimore, Maryland, for supplying hCG RIA kits.

# REFERENCES

- 1. Yalow, R.S.: Heterogeneity of peptide hormones, Recent Prog. Horm. Res. 30:597, 1974.
- Brossmer, R., Dörner, M., Hilgenfeldt, V., Leidenberger, F., and Trude, E.: Purification and characterization of human chorionic gonadotropin, FEBS Lett. 15:33, 1971.
- Canfield, R. E., Morgan, F. J., Kammerman, S., Bell, J. J., and Agosto, G. M: Studies of human chorionic gonadotropin. Recent Prog. Horm. Res. 27:121, 1971.
- Graesslin, D., Weise, H. C., and Braendle, W.: The microheterogeneity of human chorionic gonadotropin (HCG) reflected in the β-subunits, FEBS Lett. 31:214, 1973.
- Merz, W. E., Hilgenfeldt, U., Dörner, M., and Brossmer, R.: Biological, immunological and physical investigation on human chorionic gonadotropin, Hoppe-Seylers Z. Physiol. Chem. 355:1035, 1974.
- van Hell, H.: Purification and characterization of urinary HCG, in Moudgal, N. R., editor: Gonadotropins and Gonadal Function, New York, 1974, Academic Press, Inc., p. 66.
- Chan, P. K., Lee, C. Y., and Ma, L.: Purification and characterization of human chorionic gonadotropin in hydatidiform mole, in Moudgal, N. R., editor: Gonadotropins and Gonadal Function, New York, 1974, Academic Press Inc., p. 93.
- S. Wakabayashi, K., and Hattori, M.: Isoelectric focusing studies on pituitary luteinizing hormone, Protein Nucleic Acid and Enzyme (Suppl.), p. 89, 1978. (In Japanese.)
- 3. Greenwood, F. C., Hunter, W. M., and Glover, J. S.: The preparation of <sup>13</sup>I-labelled human growth hormone of high specific radioactivity, Biochem. J. 89:114, 1963.

for neurogenic atony of the urinary bladder with retention, higher titrated dosages may be needed (up to 200 mg/day)



# **MSD** announces

when higher titrated dosages are indicated

After titration, dosages as h. gh as 50 mg t.i.d. or q.i.d. have been effectively employed in neurogenic atony of the urinary bladder as well as for the treatment of postoperative and postpartum nonobstructive (functional) urinary retention.

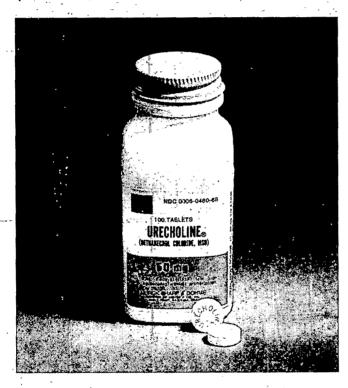
- Helps to initiate micturition and empty the bladder.
- Helps to reduce the frequency of bladder catheterization. Contraindicated in hypersensitivity to

URECHOLINE, hyperthyroidism, pregnancy, peptic ulcer, latent or active bronchial asthma, pronounced bradycardia or hypotension, vasomotor instability, coronary artery disease, epilepsy, and parkinsonism. URECHOLINE should not be used when

the strength or integrity of the gastrointestinal or bladder wall is in question or in the presence of mechanical obstruction. If necessary, the effects of the drug can be abolished promptly by atropine.

for neurogenic atony of the urinary bladder with retention, higher titrated dosages may be needed (up to 200 mg/day)

# JEW 50-mg TABLETS URECHOLINE® (BETHANECHOL CHLORIDE | MSD)



Contraindications: Hypersensitivity to Tablets URECHOLINE (Bethanechol Chloride, MSD) or to any component of Injection URECHOLINE; hyperthyroidism, pregnancy, peptic ulcer, latent or active bronchial asthma, pronounced bradycardia or hypotension, vasomotor instability, coronary artery disease, epilepsy, and parkinsonism. Should not be employed when the strength or integrity of the gastrointestinal or bladder wall is in question, or in the presence of mechanical obstruction; when increased muscular activity of the gastrointestinal tract or urinary bladder might prove harmful, as following recent urinary bladder surgery, gastrointestinal resection and anastomosis, or when there is possible gastrointestinal obstruction; in bladder neck obstruction, spastic gastrointestinal disturbances, acute inflammatory lesions of the gastrointestinal tract, or peritonitis; or in marked vagotonia.

Warnings: The sterile solution is for subcutaneous use only. It should never be given intramuscularly or intravenously. Violent symptoms of cholinergic overstimulation, such as circulatory collapse, fall in blood pressure, abdominal cramps, bloody diarrhea, shock, or sudden cardiac arrest are likely to occur if the drug is given by either of these routes. Although rare, these same symptoms have occurred after subcutaneous injection, and may occur in cases of hypersensitivity or overdosage.

**Precautions:** Special care is required in patients receiving ganglion blocking compounds because a critical fall in blood pressure may occur; usually, severe abdominal symptoms appear before there is such a fall in blood pressure. In urinary retention, if the sphincter fails to relax as the drug contracts the

bladder, urine may be forced up the ureter into the kidney pelvis; if there is bacteriuria, this may cause reflux infection.

Adverse Reactions: Abdominal discomfort, salivation, flushing of the skin ("hot feeling"), sweating. Large doses more commonly result in effects of parasympathetic stimulation, such as malaise, headache, sensation of heat about the face, flushing, colicky pain, diarrhea, nausea and belching, abdominal cramps, borborygmi, asthmatic attacks, and fall in blood pressure.

Atropine is a specific antidote. The recommended dose for adults is 0.6 mg (1/100 grain). The recommended dosage in infants and children up to 12 years of age is 0.01 mg/kg repeated every two hours as needed until the desired effect is obtained, or adverse effects of atropine preclude further usage. The maximum single dose should not exceed 0.4 mg. Subcutaneous injection of atropine is preferred except in emergencies when the intravenous route may be employed. When Injection URECHOLINE is used, a syringe of atropine sulfate should always be available.

How Supplied: Tablets, containing 5 mg, 10 mg, 25 mg, or 50 mg bethanechol chloride each, in bottles of 100 and single-unit packages of 100; Injection, 5 mg per ml, is a clear, colorless solution, and is supplied in boxes of 6 × 1-ml vials.

For more detailed information, consuit your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, PA 19486



J9URO2(426)

# FETUS, PLACENTA, AND NEWBORN

# Nonstress testing

ALLAN B. WEINGOLD, M.D. M. LYNNE YONEKURA, M.D. JANE O'KIEFFE, B.A. Washington, D. C.

Physiologic considerations on regulation of the fetal heart rate are reviewed. The types of fetal heart rate acceleration are classified and illustrated. Data from 509 patients undergoing 1,281 nonstress tests are presented, with emphasis on indications, technique, and interpretation. The nonstress test had a false negative rate lower than that of the contraction stress test. Since the false positive rate is high, a nonreactive test requires further evaluation. Progressive loss of baseline variability and decreasing frequency of accelerations appear to be early signs of fetal compromise. (Am. J. Obstet. Gynecol. 138:195, 1980.)

Kubli, in 1969, suggested that monitoring of the baseline fetal heart rate (FHR) without oxytocin stimulation might be effective in the antepartum evaluation of high-risk pregnancy. Specific description of the significance of acceleration in the FHR as a good prognostic sign for perinatal outcome is attributable to Ruttgers and associates in 1972. Trierweiler and associates, in 1976, established a strongly positive correlation between absent fetal cardiac reactivity and the positive contraction stress test, leading toward the clinical application of antepartum nonstress testing.

We present our experience with nonstress testing, and emphasize indications, technique, interpretation, and correlation with intrapartum events and perinatal outcome. We conclude that nonstress testing is the primary screening procedure for antepartum assessment of fetal well-being.

From the Department of Obstetrics and Gynecology, The George Washington University School of Medicine and Health Sciences.

Received for publication October 16, 1979.

Revised March 4, 1980.

Accepted March 27, 1980.

Reprint requests: Allan B. Weingold, M.D., Department of Obstetrics and Gynecology, 2150 Pennsylvania Ave., N. W., Washington, D. C. 20037.

# Physiologic considerations

Regulation of the FHR has been discussed in an excellent review by Martin.<sup>4</sup> Activation of the sympathetic innervation of the fetal heart results in acceleration in the rate, whereas epinephrine, because of its vasoconstrictor activity, may initially result in reflex slowing of the FHR.5 That there is also a tonic influence of the sympathetic system on the FHR is demonstrated by slowing after the administration of beta-adrenergic blocking agents. Activation of the parasympathetic autonomic system results in slowing of the FHR. Conversely, administration of atropine is followed by cardiac acceleration, which suggests a counterbalancing tonic parasympathetic influence on the FHR. In the human fetus during the last trimester, the balance of autonomic response appears to shift from sympathetic preponderance early to vagal dominance by the thirty-eighth week, with a gradual slowing in the baseline FHR.

Acceleration in the FHR may be periodic or not related to contraction. Those accelerations accompanying uterine contractions may occur during the contraction phase of the uterine pressure wave or may follow or precede a periodic FHR pattern. In the former instance, the acceleration is fairly rapid and the return to baseline is equally abrupt (Fig. 1). The most likely cause

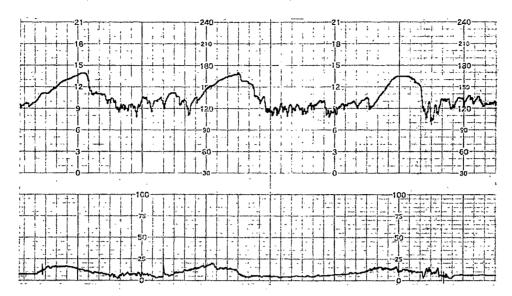


Fig. 1. Periodic accelerations occurring with contractions.

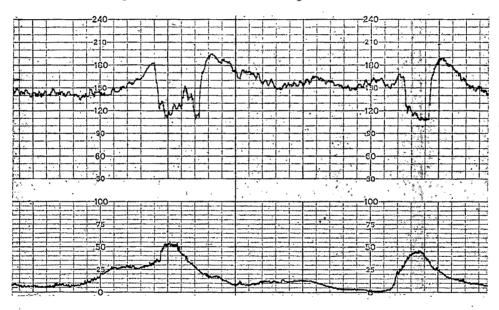


Fig. 2. Periodic accelerations preceding and following variable decelerations.

of this benign type of FHR acceleration is partial occlusion of the umbilical vein, which produces hypovolemia, hypotension, and increased FHR via the physiologic mechanism of the baroreceptor. Support for the concept is gained by the variable nature of the patterns and the association with patterns of cord compression that often appear in later labor.

Rebound accelerations that follow variable patterns may occur as short, abrupt FHR changes in the absence of fetal distress (Fig. 2). Occasionally, after prolonged cord compression, there may be more prolonged (20 to 30 seconds) smooth acceleration, which may be due to adrenal activation by hypoxia. Goodlin and Lowe<sup>7</sup> considered this overshoot pattern to be ominous.

An infrequent but more ominous pattern of acceleration consists of a small increase in FHR (5 to 15 beats per minute) beginning at or after the contraction peak, superimposed on a smooth baseline (Fig. 3). This pattern is sometimes observed preceding the appearance of late deceleration. It seems to be due to hypoxia and may represent sympathetic activation prior to the occurrence of direct hypoxic cardiac depression.

Nonperiodic FHR accelerations are the most common form of the pattern observed and are generally associated with fetal movement. These accelerations • are typically in the range of 15 to 25 beats per minute and last 10 to 30 seconds (Fig. 4). Daily fetal movements increase from the eighteenth week of gestation,

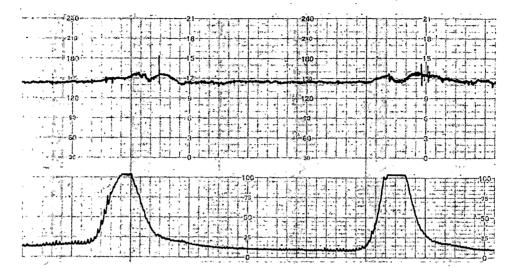


Fig. 3. Postcontraction accelerations with a fixed baseline. These often precede the appearance of late deceleration.

Table I. Antepartum FHR testing

	CST		NST	
	Patients	Test	Patients	Test
1973-1974	154	375	0	0
1975-1976	178	402	38	55
1977-1978	86*	97	509	1,281

\*CST used only for nonreactive or repetitive inadequate

and reach a maximum between the twenty-ninth and thirty-eighth week. Sadovsky and Yaffe<sup>8</sup> have determined by electromagnetic recording that approximately 87% (range, 64 to 100%) of all fetal movements are felt by the mother, and have used this capacity as a test of fetal well-being. Although nonperiodic accelerations in the absence of apparent fetal movement may be caused by lesser degrees of fetal activity, it is possible that other factors may be involved. The physiologic mechanism of these accelerations is not completely understood. That catecholamines are not responsible is suggested by the fact that accelerations are not increased during the administration of beta-agonists which regularly produce fetal tachycardia.9 The mechanism underlying these accelerations may be either a transient decrease in vagal tone or an increase in sympathetic tone, or both. From the abruptness of many of these sporadic accelerations, and the observation that they are not accompanied by a consistent change in the duration of the pre-ejection period, it is likely that the • vagal mechanism (decreased tone) predominates. 10 In any case, the presence of nonperiodic accelerations signifies an intact nervous system and a responsive myocardium.

Table II. Criteria for assessment of the NST

Reactive	Accelerations of 15 beats per minute or more above baseline, last 15 seconds or more with 5 fetal movements in 20 minutes
Nonreactive	No accelerations with fetal movements or fewer than 5 accelerations in 20 minutes; test period must be 40 minutes minimum
Sinusoidal	Oscillations occurring with a frequency of 2 to 5 cycles per minute with an amplitude of 5 to 15 beats per minute
Inadequate	Unreadable FHR data or no fetal movements recorded

Table III. Nonstress testing at George Washington University Medical Center

Year	Tests	Reactive	Nonreactive	Inadequate
1977	609	452	29	128
1978	672	587	35	50
Total	1,281	1,039	64	178
Patients	509	444	44	21

# Material and methods

During the years 1973 to 1978, a total of 2,210 antepartum fetal heart rate tests were performed on 909 high-risk obstetric patients (Table I). From 1973 to 1976, the contraction stress test (CST) was the primary surveillance test for FHR. The nonstress test (NST) was introduced at the George Washington University Hospital in 1976. Its availability resulted in an overall increase in antepartum testing, whereas the frequency cf contraction stress testing was reduced because of its use as a secondary procedure. Results of the experi-€nce with the CST were reported earlier. 11 The present study focuses on the 509 patients who underwent 1,281

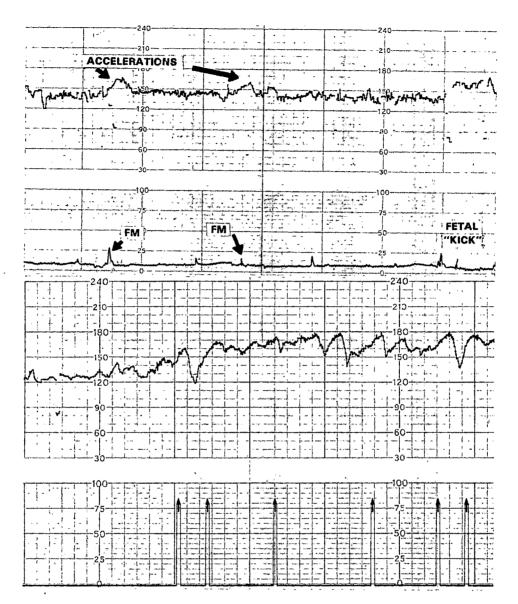


Fig. 4. Top: Reactive nonstress test with accelerations of 15 bpm. Bottom: Frequent fetal movements resulting in tachycardia and superimposed accele-ation.

NSTs in 1977 to 1978. The indications for the NST included the major high-risk factors, and this series differed from the earlier one only in the higher percentage of patients tested for postdatism, a relatively lower-risk complication that is less frequently assessed with the CST.

The nonstress testing was conducted in a manner identical with our previous protocol for contraction stress testing.11 The fetal heart rate pattern was assessed for baseline, variability, and the occurrence of any periodic acceleration or deceleration. The patient was observed for at least 40 minutes, with maternal vital signs recorded every 10 minutes. Palpation and sound stimulation were used to enhance fetal movement when this was not apparent. Fetal activity was recorded by the observer or by the patient on the uterine activity channel of the recorder. A perinatal Fellow and/or a monitoring technician performed all procedures in order to standardize technique and interpretation.

The NST was defined to include four categories (Table II). Since the procedure was employed as the primary screening test for patients at risk, a reactive test was narrowly and strenuously defined in order to reduce the incidence of false negative results. At least • five accelerations of specific amplitude and duration in a 20-minute period were required. Nonreactive tests were recorded only after 40 minutes of observation

Table IV. Reactive NST correlated with poor perinatal outcome

Patient	NST-to- delivery interval (days)	Early labor tracing and complications	Late labor tracing and complications	Apgar score	Weight (gm)	Survived
1. C. B.	1	PROM; smooth baseline; moderate variables; thick meconium	Amnionitis; severe vari- ables; bradycardia	4/5	3,540	Yes
2. J. W.	2	PROM; severe variables	Bradycardia; sinus arrest	3/6	1,380	Yes
3. C. D.	1	Flat baseline; moderate variables; thick meconium	Severe variables with late component cesar- ean section	4/6	2,100	Yes
4. J. T.	8	Bradycardia; late decele- ration; meconium	Cesarean section; nuchal cord twice	2/7	1,840	No
5. J. B.	7	Severe variables; meconi- um; accelerations with contractions	Late decelerations; gasping; cesarean section: nuchal cord	2/4	5,200	No beta-strepto- coccus sepsis
6. R. L.	3	PROM; meconium; se- vere variables	Flat baseline; severe variables; sinus arrest	1/0	3,017	No
7. N. N.	4	No fetal movements for 30 hours; thick meconium	Nuchal cord ×3; true knot tight	0/0	3,624	No
8. R. W.	7	Moderate variables	Severe variables; meco- nium	4/6	2,840	Yes

PROM: Premature rupture of membranes.

Table V. Nonreactive nonstress test correlated with poor perinatal outcome

Patient	NST-to- delivery interval (days)	CST	Early labor trazing and complications	Late labor tracing and complications	Apgar score	Weight (gm)	Survived
1. W. S.	1	Unsatisfactory	Precipitate labor	Meconium; severe variables; tachy- cardia; flat base- line	2/3	2,810	· No
2. V. C.	1	Positive	Late decelerations; cesar- ean section; oligohy- dramnios; meconium		1/4	2 <b>,</b> 605	· Yes
3. A. C.	6	Negative	Absent FHR; intra- uterine growth re- tardation		0/0	1,235	No
4. J. W.	3	Unsatisfactory	Flat baseline; severe vari- ables	Severe late decelera- tions	2/4	1,600	Yes
5. R. K.	5 .	Negative	Absent FHR; intra- uterine growth re- tardation	_	0/0	1,940	No

with manual or sound stimulation. Inadequate tests had to be differentiated from reactive and nonreactive tests. It was important to designate tests as inadequate when FHR data were not readable and to avoid interpreting artifact as acceleration. Finally, we separately defined the sinusoidal pattern, since the cyclic baseline may resemble accelerations but has grave prognostic implications.

# Results

· Of the 509 patients screened, 444 had repetitively reactive tests (Table III). Forty-four patients had 64 nonreactive tests. These will be the subject of a more detailed review. There were also 178 inadequate procedures, an incidence of 13.8%, which figure relates closely to the 10% reported by Fox and associates.12 The number of inadequate procedures had been significantly reduced in the second year of the study by increased use of sound stimulation and limitation of the number of personnel who performed the tests. In the total series, only 21 patients could not be assessed by this procedure.

We correlated the test results and perinatal outcome by including all stillbirths, early neonatal deaths, and the Apgar scores of 6 or under at 5 minutes. Eight poor outcomes were identified in the reactive NST group. In these eight patients, the fetal monitoring record in labor was reviewed in toto and the chart was scrutinized

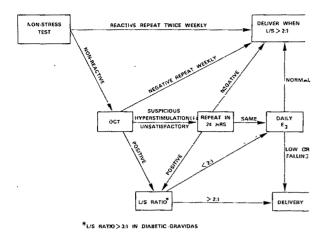


Fig. 5. Flow chart showing utilization of NST and CST in antepartum evaluation.

for clinical information (Table IV). At least five of these patients (Nos. 1, 2, 6, 7, 8) had complications of labor which were clearly unrelated to the previously reactive NSTs. Therefore, among the 444 patients with reactive tests, there were three false negative tests, for an overall incidence of 0.7%. This figure compares favorably with the 1.1% false negative test rate noted in our CST series.11

In the 21 patients (4.1%) who had persistently inadequate NSTs, there were three poor perinatal outcomes, including one neonatal death and one instance of the frequent occurrence of late decelerations during early labor.

There was a total of 64 nonreactive tests in 44 patients. The percentage of nonreactive NSTs (8.6%) is somewhat higher than the percentage of positive CSTs obtained during our earlier experience. The false positive rate with the CST was measured by the absence of late deceleration in subsequent labor (38%). In the NST evaluation, the false positive rate was calculated by the previously described poor perinatal outcome. Only five patients (Table V) met these criteria. It is interesting to note that there were two stillbirths associated with nonreactive NSTs and negative CSTs (patients 3 and 5) within 1 week of delivery. In both cases, the clinical diagnosis of intrauterine growth retardation was substantiated by autopsy. In both cases, absence of accelerations was associated with a fixed, flattened baseline pattern of heart rate which was easily readable with external cardiotachometry. We have subsequently identified four other patients with this extremely ominous pattern which calls for prompt termination of pregnancy. When a nonreactive NST was followed by a positive CST, late decelerations were found during the subsequent labor in each patient. This combination of tests suggests a very poor prognosis for vaginal delivery. Unless spontaneous labor ensues (which must be monitored in its entirety), we now opt for delivery by cesaréan section rather than oxytocin induction or stimulation (see below—persistent nonreactive NSTs).

In the other 39 patients, in whom the nonreactive NST appeared to be false positive (87%), two patterns evolved in the subsequent clinical course. In 22 patients, repeat NSTs became reactive. This conversion to reactivity is a well-documented occurrence and may be related to inadequate test periods which do not allow for significant phases of fetal sleep or rest. However, it is also possible that conversion of the nonreactive test to a reactive one may represent improvement in fetal

Among the 17 patients in whom the NST remained nonreactive on repeat assessment, the fetal monitoring tracings in subsequent labor disclosed the appearance of late deceleration in only five. More importantly, in no instance was this late deceleration associated with spontaneous, unmedicated labor. The late decelerations were apparent only with the use of oxytocin stimulation or the application of epidural anesthesia. The appearance of late decelerations may signify a compromised placental reserve, but there is no clear way of eliminating a nonphysiologic stress induced by injudicious administration of oxytocin or conduction anesthesia.

# Comment

We previously reported the relative advantages and disadvantages of contraction stress testing. 11 The procedure is time-consuming and requires the presence of a physician who is able to promptly interpret the heart rate tracings. Contraction stress testing is clearly not a cost-effective procedure, and additional disadvantages include the premature labor which may result from • oxytocin stimulation, the hypertonus which may significantly stress the fetus and lead to emergency delivery, and the nonphysiologic nature of the stress resulting in a 30% to 40% false positive test frequency.

For these reasons, nonstress testing has gained increasing acceptance as a noninvasive, low-risk procedure. In 1972, Ruttgers and associates<sup>2</sup> observed that high-risk fetuses who demonstrated acceleration with movement invariably had good outcome, whereas those with an absence of acceleration had a much poorer prognosis. Trierweiler and associates,3 in a retrospective study, reviewed 255 CSTs with regard to baseline variability and the presence of accelerations. At least 5 minutes of pre-CST baseline recording were required. This limited period of time accounted for the fact that only 75 of the 255 tests studied showed accelerations. However, none of these patients had a positive CST during subsequent administration of oxytocin. Conversely, in the 180 patients with no accelerations in the pre-CST baseline period, 25 (14%) had a subsequently positive CST. The authors proposed that nonstress monitoring could be used to replace stress testing when contraindications to the CST existed. We have extended application of it to replace the CST as a screening test (Fig. 5).

It is difficult to gain support for this view from the literature because the definition of a reactive nonstress test is not standardized. Variation is apparent particularly in (a) the number of beats per minute acceleration required, (b) the duration of the acceleration, (c) the duration of time-allowed for assessment, (d) the number of accelerations required per number of fetal movements, and (e) the use of stimulation by palpation or sound to arouse the "sleeping" fetus. Farahani and Fenton<sup>13</sup> included acceleration occurring with spontaneous contractions and interpreted reactivity as evidenced by acceleration of 10 beats per minute or more during a test period of 10 to 30 minutes. Braly and Freeman<sup>14</sup> counted only those accelerations of 20 bpm or more. Rayburn and associates 15 recorded as normal any FHR acceleration during any fetal movement over a 20-minute period. Evertson and associates<sup>16</sup> retrospectively redefined the reactive NST as two or more accelerations in a 20-minute period after noting that with these criteria there were no positive ensuing CSTs. This reduced the nonreactive percentage from 34 to 26, thereby requiring fewer CSTs. Maintaining the more rigid criteria of five accelerations in a 20-minute period, we observed only an 8:6% nonreactive rate which suggested that our screened population mix was at lower risk. Evertson and associates 16 also noted a false negative rate of 1%, which supports their conclusion that the redefined criteria did not lessen the reliability of a reactive test. We are retrospectively reviewing our data and have used the newer criteria since July 1, 1979.

A review of the literature allows some conclusions to be drawn in regard to the role of nonstress testing as the primary screening technique for antepartum fetal monitoring. Lee and associates17 recorded an excellent correlation in 324 simultaneous nonstress and stress tests. In the six patients with abnormal NSTs, suspicious or positive CSTs were obtained. In all patients with reactive tests, the CST was negative. Farahani and Fenton<sup>13</sup> observed 38 patients with a positive CST, of whom 27 (70%) had minimal or no acceleration. Conversely, among 492 patients with a negative CST, none had an absence of accelerations.

Our own experience with these testing procedures included 122 patients who underwent both tests simultaneously. In these patients, the CST was used because the NST either was inadequate or was read as nonreactive. There were 78 patients with inadequate NSTs, and two of these had positive CSTs. There were 44 patients with nonreactive tests and only six had positive CSTs (13.6%). Evertson<sup>16</sup> reported a 7.3% CST positivity with a nonreactive NST. We conclude that a nonreactive NST correlates poorly with the CST, whereas a reactive NST correlates very well with a negative CST. The fact that these tests when positive do not overlap to a greater degree is not surprising in view of their poor correlation with other antepartum indices of fetal health.11

Of greater importance is the relationship between the NST obtained within 1 week before delivery and the perinatal outcome. Adverse perinatal outcome has been variously defined in the literature. Using a broad definition of perinatal morbidity, Fox and associates<sup>12</sup> described 163 patients with negative studies, all of whom had surviving infants. Twenty-four percent (24%) of the patients had increased perinatal morbidity. In 17 patients with a positive antepartum test, all infants survived, but 59% showed increased perinatal morbidity. Rochard and associates18 reported less favorable results when they used as endpoints fetal survival, fetal distress during labor, prolonged neonatal hospitalization, and the presence of signs of intrauterine growth retardation. Of 51 babies with persistently reactive patterns, 20% had either fetal distress during labor or morbid neonatal courses. However, all survived. Of 19 fetuses who demonstrated persistently nonreactive patterns, 26% died in utero and 58% required prolonged neonatal care. Rayburn and associates15 used the 5-minute Apgar score to identify infants with acute impairment of metabolic balance. A reactive NST correlated with normal-labor monitoring tracings in 97.7% of 131 cases, and an Apgar score of 7 to 10 in an identical percentage. Ten infants born after a previously abnormal (nonreactive) test included two who were stillborn and eight who had normal Apgar scores. Rayburn and associates concluded that the NST was a reliable primary screening tool for monitoring fetal well-being. Their study documents three infants in whom the NST appeared to be falsely negative: for two of these infants there were late decelerations during labor. Our own data substantiate this conclusion. We report a false negative rate of 0.7%, which is lower than our CST rate of 1.1%. Nevertheless, we agree with Evertson and associates<sup>16</sup> that ultrahigh-risk patients, such as diabetic gravidas, should be tested twice weekly -(Fig. 5).

Considerable debate centers on the issue of which procedure, contraction stress testing or nonstress testing, is an earlier detector of fetal distress. This report does not allow resolution of that question, since we have demonstrated nonreactive NSTs with negative . CSTs (patients 3 and 5, Table V) and, conversely, have observed positive CSTs with good baseline variability and accelerations with fetal movement. Since the latter is almost invariably associated with good perinatal outcome, we speculate that these are nonphysiologic, false positive CSTs. Clinically, our impression is that serial nonstress testing that demonstrates a progressive decrease in variability and frequency of accelerations is the earliest indicator of distress and has preceded positive contraction stress testing in the limited number of cases encountered.

Summary. The predictability of antepartum testing of fetal heart rate is complicated by the criteria used for measuring perinatal outcome and by the fact that events occur in labor which are unrelated to information obtained before labor. In the data presented from our own experience, the following observations appear to be valid, given the above-noted limitations.

The NST test is technically easier to perform than the oxytocin challenge test and has no inherent risk for the patient and/or her fetus by the imposition of a potentially unphysiologic stress. Its simplicity and availability in the ambulatory-care setting allows twice weekly screening of ultrahigh-risk patients.

A reactive NST is at least equally predictive of good perinatal outcome as is a negative CST.

The percentage of inadequate NSTs can be reduced to the level of unsatisfactory CSTs by rigidly defining the criteria for readability, by extending the observation period to allow for fetal rest-sleep periods, and by stimulating the fetus manually or by transabdominal sound.

Induced "reactivity" by stimulation is equally as relevant as spontaneous reactivity.

The false positive NST occurs with significantly greater frequency than the false positive CST.

These data would suggest that the NST can be used as the primary screening tool to measure the "respiratory activity" of the placenta, and this has been implemented on our service. The appearance of nonreactivity before the presence of a positive CST suggests that the NST may be an earlier, although less specific, indicator of in utero compromise.

The high false positive incidence of the NST generally requires confirmation by the CST or other indices of fetal distress. Nevertheless, when a pulmonary mature infant has a fixed baseline nonreactive NST, verified within 12 to 24 hours, we will terminate the pregnancy.

The fetus with both a nonreactive NST and a positive CST does not tolerate induction or stimulation of labor and has a poor prognosis for uncomplicated vaginal delivery.

Finally, it appears that this is one of those rare times in the field of medicine when a simpler, less expensive, and safer test can effectively replace its predecessor as a widely applied diagnostic procedure.

# REFERENCES

- 1. Kubli, F. W., Kaeser, O., and Henselmann, M.: In Pecile, A., and Finze, C., editors: The Feto-Placental Unit, Amsterdam, 1969, Excerpta Medica Foundation, p. 323.
- 2. Ruttgers, H., Kubli, E., Haller, U., et al.: Die Anterpartale Fetale Herzfrequenz. I. Verhalten von Grundfrequenz, Fluktuation und Dezeleration in Schwangerschaft, Z. Geburtshilfe Perinatol. 176:294, 1972.
- Trierweiler, M. W., Freeman, R. K., and James, J.: Baseline fetal heart rate characteristics as an indicator of fetal status during the antepartum period, Am. J. OBSTET. Gynecol. 125:618, 1976.
- 4. Martin, C. B.: Regulation of the fetal heart rate and genesis of FHR patterns, Semin. Perinatol. 2:131, 1978.
- 5. Dawes, G. S.: Foetal and Neonatal Physiology, Chicago, Year Book Medical Publishers, Inc., 1968, chap. 8.
- 6. Renou, P., Newman, W., and Wood, C.: Automatic control of fetal heart rate, Am. J. OBSTET. GYNECOL. 105:949,
- 7. Goodlin, R. C., and Lowe, E. W.: A functional umbilical cord occlusion heart rate pattern, Obstet. Gynecol. 43:22,
- 8. Sadovsky, E., and Yaffe, H.: Daily fetal movement recording and fetal prognosis, Obstet. Gynecol. 41:845, 1973.
- 9. Nochimson, D. J., Riffel, H. D., Yeh, S. Y., et al.: The effects of ritodrine hydrochloride on uterine activity and the cardiovascular system, Am. J. OBSTET. GYNECOL. 118:523, 1974.

- 10. Murata, Y., and Martin, C. B.: Systolic time intervals of the fetal cardiac cycle, Obstet. Gynecol. 44:224, 1972.
- Weingold, A. B., DeJesus, T. P. S., and O'Kieffe, J.: Oxytocin challenge test, Am. J. OBSTET. GYNECOL. 123:466,
- 12. Fox, H. E., Steinbrecher, M., and Repton, B.: Antepartum fetal heart rate and uterine activity studies, Am. J. OBSTET. GYNECOL. 126:61, 1976.
- 13. Farahani, G., and Fenton, A. N.: Fetal heart rate acceleration in relation to the oxytocin challenge test, Obstet. Gynecol. 49:163, 1977.
- 14. Braly, P., and Freeman, R. K.: The significance of FHR reactivity with a positive OCT, Obstet. Gynecol. 50:689,
- 15. Rayburn, W. F., Duhring, J. L., and Donaldson, M.: A study of fetal acceleration tests, Am. J. Obstet. Gynecol. **132:**33, 1978.
- 16. Evertson, L. R., Gauthier, R. J., Schifrin, B. S., and Paul, R. H.: Antepartum fetal heart rate testing. I. Evolution of the nonstress test, Am. J. Obstet. Gynecol. 133:29, 1979.
- 17. Lee, C. Y., DeLoreto, P. C., and Logrand, B.: Fetal activity acceleration determination for the evaluation of fetal reserve, Obstet. Gynecol. 48:19, 1976.
- 18. Rochard, F., Schifrin, B. S., Goupil, F., Legrand, H., Blottiere, J., and Sureau. C.: Nonstressed fetal heart rate monitoring in the antepartum period, Am. J. OBSTET. GYNECOL. 126:699, 1976.

# Intravenous dexamethasone for prevention of neonatal respiratory distress: A prospective controlled study

BRUCE K. YOUNG, M.D., F.A.C.O.G.
STEVEN A. KLEIN, M.D., F.A.C.O.G.
MIRIAM KATZ, M.D.
STEPHEN J. WILSON, M.D.
GORDON W. DOUGLAS, M.D., F.A.C.O.G.
New York, New York

A trial of intravenous dexamethasone for prevention of neonatal respiratory distress syndrome was carried out prospectively. There were 112 treated and 188 control patients, matched for gestational age, birth weight, rupture of membranes, and antepartum diagnosis. No short-term deletericus effects on mother or infant were demonstrable. There was an increased incidence of cesarean section and puerperal infection in the treated patients. This was not related to the steroid therapy. There was no increased incidence of infection in the treated neonates. At 28 to 33 weeks' gestation, the treated newborn infants had one half the perinatal mortality and one fourth the incidence of severe respiratory distress syndrome seen in the controls. Under 28 weeks, and from 34 to 36 weeks, no difference between treated and control groups was observed. Intravenous dexamethasone is effective in reducing perinatal mortality from respiratory distress syndrome in premature infants delivered between 28 and 33 weeks' gestation. (Am. J. OBSTET. GYNECOL. 138:203, 1980.)

DESPITE extensive research and much clinical progress, prematurity remains the leading cause of perinatal mortality in the United States. Respiratory distress syndrome (RDS) is the major complication associated with prematurity. Although there have been many advances in the treatment of neonates with RDS, it is still associated with a 35% mortality rate and approximately 12,000 neonatal deaths yearly in this country.<sup>1</sup>

The discovery of pulmonary surfactant in 1955² was followed by the observation that fatal neonatal RDS was associated with low levels of surfactant in autopsy studies.³ In 1969, Liggins observed that ACTH, cortisone, or dexamethasone given to fetal sheep at 120 days accelerated lung expansion because of an increase in surface-active material.⁴ Subsequent studies with the

From the Division of Maternal-Fetal Medicine,
Department of Obstetrics and Gynecology, New York
University School of Medicine, and Bellevue Hospital.
Received for publication December 21, 1979.
Revised March 17, 1980.
Accepted March 28, 1980.
Reprint requests: Bruce K. Young, M.D., Department of
Obstetrics and Gynecology, 530 First Avenue, Suite 5G,

use of glucocorticoids in premature lambs, rabbits, and primates have confirmed this observation. 5-7

The initial clinical trial of prenatal corticosteroid treatment of women at risk for preterm delivery was reported by Liggins and Howie in 1972.8 In a large, prospective study, they observed a significant reduction in RDS and neonatal mortality in pregnancies treated with intramuscular betamethasone, compared to placebo-treated control pregnancies. This difference was most significant in pregnancies in which delivery was between 28 and 32 weeks when the treatment-to-delivery interval was more than 1 day and less than 7 days. No adverse effects on neonates or mothers were noted. There was no control of patient selection into the study other than that of risk of preterm delivery, so that differences in outcome may have been influenced by antenatal complications. Subsequent clinical trials have confirmed Liggins and Howie's observations, 9-11 but these latter studies have involved fewer cases, particularly between 27 and 33 weeks. In most studies, the treatment and control groups were small and unmatched, thus limiting the conclusions drawn. A major factor influencing perinatal outcome that has not been directly addressed by these studies is premature rupture of the membranes (PROM). Premature rupture of

New York, New York, 10016.

204 Young et al.

**Table I.** Comparison of dexamethasone-treated and control groups

	Steroid (%)	No steroid (%)
No. of cases	112	188
Parity (X)*	$1.2 \pm 0.3$	$1.2 \pm 0.2$
Age $(\overline{X})^*$	$26.2 \pm 2.4$	$25.5 \pm 2.6$
No premature rupture of mem- branes	61 (54)	126 (67)
Premature rupture of membranes	51 (46)	62 (33)
Prolonged rupture of membranes (>24 hours)	44/51 (86)	44/62 (71)
Premature labor	51 (46)	102 (54)
Diabetes (A, B, C)	5 (4.4)	3 (1.6)
Hypertension	6 (5.4)	18 (9.6)
Twins	7 (6.3)	10 (5.3)
Other	5 (4.5)	7 (3.9)

<sup>\*</sup> $(\overline{X} \pm SE)$ .

the membranes prior to the thirty-fourth week of pregnancy poses conflicting problems in management. First, the risk of prematurely delivering the incompletely developed fetus calls for expectant management, while, on the other hand, the risk of serious fetal and maternal infection calls for aggressive management. Antenatal treatment with glucocorticoids, given over a short interval to accelerate fetal lung maturity, may permit early delivery in these cases so that infection can be avoided. There is one instance in which prenatal treatment with betamethasone in cases of PROM reduced the incidence and severity of RDS without increasing perinatal infection.12 The study population consisted of only 27 treated cases and 16 controls, and treatment and control groups were not matched for antenatal complications, thus preventing firm conclusions from the study.

The present study prospectively evaluated dexamethasone PO<sub>4</sub>\* administered to patients at risk for premature delivery between 27 and 33 weeks. The investigation was designed to determine the effect of dexamethasone treatment on the incidence and severity of RDS in matched groups, and the immediate risks to mother and fetus.

# Material and methods

All patients at risk for premature delivery at Bellevue and New York University Hospitals were evaluated for dexamethasone therapy. Antenatal gestational dating was assessed by menstrual history and ultrasonography. Patients with gestations between 27 and 33 weeks were offered dexamethasone after informed consent was obtained. Patients with intrauterine infection on admission to the hospital were excluded from

the study. Three hundred patients were studied: 112 treated patients and 188 matched controls (Table I). Whenever possible, amniotic fluid was obtained transabdominally under ultrasound, or transcervically with PROM. Fluid was analyzed for lecithin/sphingomyelin (L/S) ratio and was cultured.

All patients in early labor without PROM were given intravenous alcohol to arrest labor, as suggested by Fuchs and associates.<sup>13</sup> In addition, 12 mg of dexamethasone PO<sub>4</sub> was given by intravenous infusion over 15 minutes. This dosage was repeated in 24 hours. Repeated courses of treatment were given if delivery had not occurred by 7 days and the pregnancy was less than 34 weeks. Patients with maternal or fetal indications for early delivery in the absence of labor were treated with the same infusions of dexamethasone, and were delivered 1 to 7 days after the last dose unless the membranes were ruptured.

PROM was diagnosed by direct visualization, as well as pH testing, ferning, and glucose and protein tests on amniotic fluid. No patient with PROM was given drugs to arrest labor or prophylactic antibiotics. Patients with PROM who were not in labor were given 12 mg of dexamethasone intravenously on admission. This was repeated in 12 hours. Delivery efforts commenced 12 hours after the second dose, with delivery between 24 and 48 hours after PROM. All patients were monitored by continuous external recording of fetal heart rate (FHR), serial temperatures, and complete blood counts. Patients who developed intrauterine infection during treatment were delivered promptly. Patients with PROM who were not given steroids were delivered 24 to 48 hours after rupture of the membranes. All patients were given an intravenous infusion of 5% dextrose on admission, but only the treated group received dexamethasone in the infusion.

At delivery, the infant's weight, Apgar score, and gestational age by Dubowitz scoring were recorded by the neonatal staff. Assessment of weight for gestational age was based on previously published growth curves and physical examination. <sup>14</sup> All neonates were observed in a specialized intensive-care nursery for signs of RDS and other complications. RDS was diagnosed on the basis of clinical guidelines and radiologic findings. Neonates who required postive-pressure controlled ventilation with high concentrations of oxygen (FiO<sub>2</sub> of more than 50%) were considered to have severe RDS.

Neonatal infection was diagnosed on the basis of clinical findings and the recovery of pathogens on central or peripheral culture. Neonates who died were autopsied by a team of pediatric pathologists.

Maternal infection was based on standard morbidity

<sup>\*</sup>Decadron, Merck, Sharp & Dohme.

Table II. Comparison of neonates, by sex, for gestational age between steroid and control groups

C - 1-1'1	St	eroid	Co	ntrol	
Gestational age (weeks)	Male	Female	Male	Female	p
26-27	6	2	7	5	N/S
28-30	12	8	19	17	N/S
31-32	15	13	26	23	N/S
33-34	14	19	27	31	N/S
35-36	4	7	7	13	N/S
Male/female	- 1	.04	0	.97	N/S

N/S = Not significant.

in addition to clinical and bacteriologic findings. Severe infection was defined by fever over 101° F (38.3° C) or positive blood cultures. Statistical significance was determined by chi-square analysis or Student's t test where applicable.

### Results

Three hundred gravidas at risk for premature delivery between 27 and 33 weeks' gestation were studied prospectively. Of those patients, 112 received dexamethasone, and 188 did not receive dexamethasone (controls). Otherwise, clinical management of each high-risk patient was essentially the same in the two groups. Premature rupture of the membranes (PROM) occurred in 51 (46%) of the treated patients and in 62 (33%) of the controls. This difference was not statistically significant. The treated and control groups were well matched. There were no significant differences in the frequency of conditions believed to influence fetal lung maturation, such as PROM beyond 24 hours, diabetes, chronic hypertension, and twin gestation. In addition, in both the dexamethasone-treated and control groups, there was one patient with renal disease, chronic vaginal bleeding, and suspected growth retardation. Two patients in the treated group and four in the control group had Rh isoimmunization. Chi-square analysis revealed no significant difference between the treated and control groups (Table I).

Neonates in the treated and control population also were well matched. Three hundred and twelve infants were delivered: one hundred and eighteen in the dexamethasone group, and 194 controls. Two hundred and seventy-four were appropriate for gestational age and without major malformations. Birth weight for gestational age was closely matched from 26 to 36 weeks (Fig. 1). Sex distribution of the neonates were not significantly different between the two study groups (Table II). The frequencies of low Apgar scores also were similar in the groups, 15.2% for the steroid group and 16% for the controls. The occurrence of

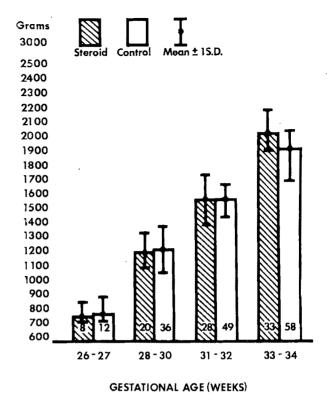


Fig. 1. Neonatal birth weight vs. gestational age between steroid and control.

neonatal depression, defined as a 5-minute Apgar score below 7, significantly increased the risk and severity of RDS in both groups, compared to neonates with Appar scores of 7 or more (p < 0.01) (Table III). The effect of low Apgar score on RDS was seen in both groups, although it was less in the group treated with steroids.

There was one stillbirth in the series. This occurred in the treated group, prior to labor in an infant with major congenital anomalies. The uncorrected mortality rate (PNM) was 127/1,000 in the dexamethasonetreated group, and 175/1,000 in the control group, which clearly demonstrates the high-risk nature of the patient population under study.

Between 28 and 33 weeks, dexamethasone treatment reduced the perinatal mortality significantly (p < 0.05). There was no statistically significant difference in mortality at 26 to 27 or 34 to 36 weeks between treated and control groups (Table IV). Moreover, dexamethasone therapy significantly reduced the frequency and severity of RDS among the 71 treated fetuses compared to the 108 control fetuses delivered between 28 and 33 weeks (p < 0.001). No reduction in RDS risk was noticed prior to 28 weeks, and only a limited reduction in RDS frequency, but not severity, was observed after 33 weeks (Table V). Dexamethasone

	Steroids		Contr			
	5-min Apgar	5-min Apgar		5-min Apgar	5-min Apgar	
	6 or less (%)	7 or more (%)	į,	6 or less (%)	7 or more (%)	þ
RDS Severe RDS	11/15 (73) 6/15 (40)	25/84 (30) 4/84 (4.7)	<0.05 <0.001	28/35 (80) 21/35 (60)	83/140 (59) 38/140 (27)	<0.05 <0.01

Table III. Effect of low 5-minute Apgar score on the incidence and severity of RDS among steroid and control groups

**Table IV.** Effect of steroid treatment on perinatal mortality, by gestational age at delivery

Gestational age (weeks)	Steroid (%)	No steroid ` (%)	p
26-27	7/8 (87.5)	6/12 (50.0)	N/S
28-33	7/73 (9.6)	26/124 (21)	< 0.05
34-36	0/36 (0)	2/60 (3.3)	N/S

treatment reduced the incidence and severity of RDS whether membranes were (p < 0.05) or were not (p < 0.01) ruptured (Table VI). A duration of PROM beyond 24 hours was associated with a trend toward a lesser incidence of RDS in the group not treated with dexamethasone (Table VII). This is consistent with the limited statistical significance of the steroid effect on RDS with PROM. Both sets of data confirm the clinical observation of a protective effect of PROM against RDS.

The timing of delivery in relation to the initiation of treatment was important. Those fetuses whose treatment interval from first dose of dexamethasone to delivery was over 24 hours had significantly less RDS than if delivery occurred before 24 hours, 27% versus 73% (p < 0.001). No significant difference in RDS occurred when the interval between first dose and delivery was 25 to 48 hours compared to 49 to 96 hours. Thus, no benefit accrued from delay beyond 48 hours. However, an interval of less than 24 hours to delivery reduced the benefit of steroid therapy, probably because of insufficient time for drug effect, and possibly insufficient dose.

No short-term adverse effects related to dexamethasone treatment were noticed among the neonates. No specific hazard of adrenal insufficiency, hyperbilirubinemia, or hypoglycemia was noticed in the dexamethasone-treated neonates, compared to controls. Among the dexamethasone-treated fetuses there was no increase in stillbirth or fetal distress rates, even when the mothers were diabetic or had controlled hypertensive disease. There was no increase in the frequency or severity of neonatal infection in the dexamethasone group, nor did these neonates show an im-

**Table V.** Incidence and severity of RDS in steroid-treated and control groups

	Steroid (%)	No steroid (%)	þ
26-27 weeks			
RDS	5/8 (63)	7/12 (58)	N/S
Severe RDS	2/8 (25)	3/12 (25)	N/S
28-33 weeks	, ,		
RDS	29/71 (41)	80/108 (74)	< 0.001
Severe RDS	8/71 (11)	50/108 (46)	< 0.0001
34-36 weeks	` ,	` '	
RDS	2/20 (10)	25/55 (45)	< 0.02
Severe RDS	0/20 (0)	6/55 (11)	N/S
Total RDS	36/99 (36)	112/175 (64)	< 0.001
Total severe RDS	10/99 (10)	59/175 (34)	< 0.001

paired ability to respond clinically to infection (Table VIII). One perinatal death due to sepsis and immaturity occurred in the dexamethasone group. This fetus died at 27 weeks, 4 hours post partum, with Klebsiella pneumonia after 38 hours of PROM. There were three deaths from sepsis in the control group. In two of these cases the PROM was more than 48 hours, and in both, Group B beta hemolytic streptococcus was recovered from the maternal cervix and neonate's blood. Neutrophil infiltration of the membranes was evident in both cases. The third case of fatal sepsis was associated with ambilical catheter infection. The risk of neonatal in-Fection was 21% (21/102) in patients with PROM, and 7.7% (12/155) in patients with intact membranes p < 0.01). Furthermore, the risk of infection doubled to 42% (13/31) as the duration of PROM lengthened beyond 48 hours (p < 0.01).

There were no maternal deaths. There was an increased infectious morbidity among the dexamethasone-treated patients, 28% vs. 15% (p < 0.02), but no increase in severe infections compared to control patients. However, cesarean section was performed more often (p < 0.01), especially with PROM (p < 0.001), in the dexamethasone series. Cesarean section (40%) and FROM beyond 24 hours (65%) were associated with the most significant incidences of maternal infection regardless of steroid treatment. When patients in both dexamethasone and control groups were matched for

Table VI. Effect of steroid treatment on RDS in fetuses with PROM or intact membranes (28 to 33 weeks)

	PR	ОМ	Intact me		Intact membranes	
	Steroid (%)	Control (%)	p _	Steroid (%)	Control (%)	þ
RDS Severe RDS	17/38 (45) 4/38 (11)	25/35 (71) 14/37 (58)	<0.05 <0.05	12/32 (38) 4/32 (13)	55/72 (76) 36/72 (50)	<0.01 <0.01

Table VII. Effect of duration of PROM on RDS among neonates delivered between 27 and 36 weeks

,	<24	<24 hours		24 to 48 hours		>48 hours	
	RDS (%)	Severe RDS (%)	RDS (%)	Severe RDS (%)	RDS (%)	Severe RDS (%)	
Steroids							
26-27 wk	0/1	0/1	2/4	2/4	1/2	1/2	
28-33 wk	4/6 (67)	1/6 (17)	9/23 (59)	3/23 (13)	4/9 (44)	0/9 (0)	
34-36 wk	0/1	0/1	0/4	0/4	0/1	0/1	
Total	4/8 (50)	1/8 (13)	11/13 (36)	5/31 (35)	5/12 (42)	1/12 (8)	
No steroids				*			
26-27 wk	1/1	1/1	2/2	1/2	2/4	1/4	
28-33 wk	9/11 (82)	6/11 (55)	9/12 (75)	5/12 (42)	7/14 (50)	3/14 (21)	
34-36 wk	2/6	1/6	3/7	0/7	1/4	1/4	
Total	12/18 (67)	8/18 (44)	14/21 (33)	6/21 (29)	10/22 (45)	5/22 (23)	

Table VIII. Effect of steroid treatment on neonatal infection

•	Steroid (%)	No steroid (%)	Þ
All infections	11/108 (10)	29/176 (16)	N/S
Central infections	7/108 (6.4)	15/176 (8.5)	N/S
•	Steroid and PROM (%)	No steroid and PROM (%)	Þ
All infections	10/51 (20)	17/62 (27)	N/S
Central infections	7/51 (14)	9/62 (15)	N/S
•	Steroid and no PROM (%)	No steroid, no PROM (%)	Þ
All infections	1/57 (1.8)	12/114 (10.5)	N/S
Central infections	5/57 (8.8)	6/114 (5.3)	N/S

PROM and mode of delivery, there were no differences in infection rates: 63% for the treated group, and 75% for the untreated group. Gravidas who received dexamethasone and who developed systemic infection responded satisfactorily to appropriate antibiotics. The type of infection was similar in both groups, with endometritis diagnosed in 73% of the steroid-treated group and in 83% of the control group (Table IX). No recrudescence of latent tuberculosis was noted among five patients with prior history of pulmonary tuberculosis.

# Comment

Antenatal dexamethasone therapy reduced the incidence and severity of RDS among infants delivered at 28 to 33 weeks' gestation. Prior to 28 weeks, there was no significant benefit from dexamethasone. This was most likely due to the immaturity of fetal lung alveoli at that gestational age. In addition, other problems of prematurity may reduce neonatal survival before 28 weeks. Beyond 34 weeks' gestation, mortality from

Table IX. Type of maternal infection

-	Steroid (%) N = 29	Control (%) N = 15	p
Endometritis	24 (83)	11 (73)	N/S
Urinary tract infection	2 (6.9)	3 (20)	N/S
Other	3 (10.3)	1 (6.7)	N/S
Sepsis	3 (10.3)	2 (13.3)	N/S

RDS is uncommon, and routine treatment with dexamethasone seems to be unwarranted. Although steroidinduced changes in the L/S ratio of amniotic fluid was examined in this series, an insufficient number of pretreatment and posttreatment fluids was obtained to permit adequate statistical analysis. The clinical impression was that the L/S ratio was often accelerated by dexamethasone treatment.

There were no demonstrable adverse effects on the fetus or neonate. Dexamethasone therapy did not increase the frequency or severity of neonatal infection. A progressive risk of infection with PROM was observed in the patients studied. This problem was attacked by rapid induction of lung maturation and aggressive delivery. Delivery was achieved by 24 to 36 hours after commencing steroids in patients with PROM. With intact membranes, delivery was at least 24 hours but less than 7 days after the last dose of dexamethasone. Those infants who became infected after steroid treatment showed no impairment of response to infection. Steroid therapy was not associated with fetal distress, even in patients with hypertensive disease and diabetes. However, cesarean section was used liberally in both treated and control groups.

In vivo studies have shown that the placenta metabolizes corticosteroids, and that dexamethasone readily crosses the placenta.15 Dexamethasone is about 20 times more potent than cortisol. The intravenous infusion method was chosen to permit rapid pharmacologic action. The mothers occasionally showed flushes or paresthesias as side effects, but no major toxicity was noticed. The major maternal risk of steroid therapy is the possibility of a diminished resistance to infections and potential reactivation of latent infection. The present study did not find an increase in maternal infection related to steroid treatment. However, cesarean section was performed more often among steroid-treated patients for fetal indications other than fetal distress. Cesarean section and PROM beyond 24 hours were the major significant risk factors for maternal infection in this study. When this was taken into consideration, the use of steroid did not alter infection rates with or without ruptured membranes. Mothers who received dexamethasone did not have an increased frequency of septicemia, and they responded satisfactorily to antibiotics. No recrudescence of latent infection, such as tuberculosis, was noted. Thus, although the overall infection rate was greater in the steroid group, this was not demonstrably related to the steroid therapy.

There may be a synergistic effect between PROM and dexamethasone to accelerate lung maturity. There is evidence that PROM beyond 48 to 72 hours will produce an elevation of cortisol in amniotic fluid and umbilical cord blood, and is beneficial for RDS outcome. However, PROM beyond 24 to 48 hours was associated with a significant increase in maternal and neonatal infection. Two perinatal deaths due to sepsis occurred in cases with PROM for more than 48 hours. Thus, the critical period for preventing infection seems to be the 24 to 48 hours after PROM.

Dexamethasone treatment was clearly beneficial in this series. On the basis of these findings, it is proposed that all patients at significant risk for preterm delivery from 28 to 33 weeks be managed as follows: (1) Estimate gestational age. (2) Evaluate for PROM. (3) Assess fetal pulmonary maturity. (4) Obtain informed consent for dexamethasone therapy. (5) With PROM: Give dexamethasone PO4, 12 mg intravenously every 12 hours, two times, with planned delivery at least 12 hours after the second dose. If labor occurs or infection arises, delivery is indicated. (6) With intact membranes: Give tocolytic drugs as needed. Give dexamethasone, 12 mg every 24 hours, twice with delivery at least 24 hours after the last dose.

The use of this protocol in a controlled, prospective study of 300 patients demonstrated that dexamethasone therapy is effective in reducing perinatal mortality from RDS in premature infants. The perinatal mortality between 28 and 33 weeks' gestation was 21% for the controls and 9.6% for the steroid-treated group. Thus, steroid treatment more than halved the perinatal mortality. The incidence of RDS at 28 to 33 weeks was 74% for the controls and 41% for the steroid-treated group. Severe RDS had an incidence of 46% in the control group, and only 11% in the steroid-treated group. The benefit of steroid therapy is unequivocally seen as a fourfold reduction in the occurrence of severe RDS, with a concomitant halving of the perinatal mortality between 28 and 33 weeks of pregnancy.

The risks which must be considered are short term and long term. Short-term maternal risks appear to be limited to increased use of cesarean section delivery, and an increased incidence of infection. These factors are related more to each other and the high-risk patients studied than to the dexamethasone therapy. No short-term fetal risks were demonstrable in this series. The long-term risks to mother and child remain indeterminate at present. Encouraging data have been reported by Liggins<sup>16</sup> in patients followed up to 5 years after treatment. Nevertheless, caution must be exercised as 10- and 20-year data are accumulated. Therapeutic enthusiasm must be restrained until safety, as well as efficacy, is proven. Only long-term follow-up studies can provide such reassurance, and there is none thus far.

# REFERENCES

- Farrell, P. M., and Wood, R. E.: Epidemiology of hyaline membrane disease in the United States: Analysis of national mortality statistics, Pediatrics 58:167, 1976.
- Pattle, R. E.: Properties, function, and origin of the alveolar lining layer, Nature (Lond.) 175:1125, 1955.
- 3. Avery, M., and Mead, J.: Surface properties in relation to

- atelectasis and hyaline membrane disease, Am. J. Dis. Child. 97:517, 1959.
- 4. Liggins, G. C.: Premature delivery of foetal lambs infused with glucocorticoids, J. Endocrinol. 45:515, 1969.
- 5. Delemos, R. A., Shermata, O. W., Knelson, J. H., et al.: Acceleration of appearance of pulmonary surfactant in the fetal lamb by administration of corticosteroids, Am. Rev. Respir. Dis. 102:459, 1970.
- 6. Kotas, R. V., and Avery, M. E.: Accelerated appearance of pulmonary surfactant in the fetal rabbit, J. Appl. Physiol. 30:358, 1971.
- 7. Delemos, R. A., and McLaughlin, G. W.: Induction of the pulmonary surfactant in the fetal primate by the intrauterine administration of corticosteroids. Pediatr. Res. 7:425, 1973.
- 8. Liggins, G. C., and Howie, R. N.: A controlled trial of antepartum glucocorticoid treatment for the prevention of the respiratory distress syndrome in premature infants, Pediatrics 50:515, 1972.
- 9. Caspi, E., Schreyer, P., Weintraub, Z., et al.: Prevention of the respiratory distress syndrome in premature infants by antepartum glucocorticoid therapy, Br. J. Obstet. Gynaecol. 83:187, 1976.

- 10. Block, M. F., Kling, O. R., and Crosby, W. M.: Antenatal glucocorticoid therapy for the prevention of respiratory distress syndrome in the premature infant, Obstet. Gynecol. 50:186, 1977.
- 11. Taeusch, H. W., Frigoletto, F., Kitzmiller, J., et al.: Risk of respiratory distress syndrome after prenatal dexamethasone treatment, Pediatrics 63:64, 1979.
- 12. Mead, P. B., and Clapp, J. F.: The use of betamethasone and timed delivery in management of premature rupture of the membranes in the preterm pregnancy, J. Reprod. Med. 19:3, 1977.
- 13. Fuchs, F., Fuchs, A. R., Poblete, U. F., et al.: Effect of alcohol on threatened premature labor, Am. J. OBSTET. GYNECOL. 99:627, 1967.
- 14. Lubchenco, L. O., Hansman, C., Dressler, M., et al.: Intrauterine growth as estimated from liveborn birthweight data at 24 to 42 weeks' gestation, Pediatrics 32:793, 1963.
- 15. Levitz, M., Jansen, V., and Dancis, J.: The transfer and metabolism of corticosteroids in the perfused human placenta, Am. J. Obstet. Gynecol. 132:363, 1978.
- 16. Liggins, G. C.: Personal communication.

# Clinical significance of perceptible fetal motion

WILLIAM F. RAYBURN, M.D.

Columbus, Ohio

The monitoring of fetal activity during the last trimester of pregnancy has been proposed to be useful in assessing fetal welfare. The maternal perception of fetal activity was tested among 82 patients using real-time ultrasonography. All perceived fetal movements were visualized on the scanner and involved motion of the lower limbs. Conversely, 82% of all visualized motions of fetal limbs were perceived by the patients. All combined motions of fetal trunk with limbs were perceived by the patients and described as strong movements, whereas clusters of isolated, weak motions of the fetal limbs were less accurately perceived (56% accuracy). The number of fetal movements perceived during the 15-minute test period was significantly (p < 0.001) greater in pregnancies with ruptured amniotic membranes (9.2  $\pm$  1.8) than in those with intact membranes (4.2  $\pm$  0.6). A favorable neonatal outcome was more common (p < 0.01) when recent visualized strong fetal motion was present (44 of 45 cases) than when it was absent (five of 10 cases). These findings reveal that perceived fetal motion is: (1) reliable; (2) related to the strength of lower limb motion; (3) increased with ruptured amniotic membranes; and (4) reassuring if considered to be active. (AM. J. OBSTET. GYNECOL. 138:210, 1980.)

MATERNAL PERCEPTION of daily fetal activity has been proposed to be useful in assessing fetal welfare.<sup>2–5</sup> However, the reliability of the mother's counting of daily fetal movements has been questioned. Sadovsky and associates<sup>4</sup> reported that the patient's subjective sensation registered about 87% of any fetal motion recorded by an electromagnetic recording device. Gettinger and associates<sup>1</sup> found, in 40 pregnant women, a highly significant correlation between fetal motion visualized by real-time ultrasonography and the patient's subjective sensation. However, large individual variations were present, and many women appeared to have a reduced sensitivity to fetal movement.

The purpose of this investigation was to relate fetal motion perceived by the patient to objective ultrasound assessment of fetal motion in pregnancies with intact and ruptured amniotic membranes. The different types of perceptible fetal movements in each pregnancy were then related to the subsequent neonatal outcome.

From the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, The Ohio State University College of Medicine.

Received for publication January 10, 1980.

Revised April 29, 1980.

Accepted May 12, 1980.

Reprint requests: William Rayburn, M.D., Department of Obstetrics and Gynecology, The Ohio State University Hospital, 410 West 10th Ave., Columbus, Ohio 43210.

# Material and methods

Patients who were receiving obstetric care at The Ohio State University Hospital Clinics during the third trimester (28 to 43 weeks) were examined. Any complication during the antepartum period was recorded, including the presence of documented prematurely ruptured amniotic membranes.

All antepartum examinations were performed in the outpatient clinic or labor hall during a 15-minute test period in the late morning and afternoon. An EkoLife SKI scanner and an ADR real-time scanner (Model 2130) were used. Fetal motion was visualized along the longitudinal axis of the fetus, particularly at the level of the fetal abdomen and lower extremities. The patient was instructed to describe the strength (strong or weak) and type ("kick," "stretch," "flutter," "rollover," "balling-up") of any perceived fetal movement. The ultrasound scanner image was visible only to the examiner.

The neonatal outcome (favorable or unfavorable) was assessed when delivery occurred within 5 days after the ultrasound procedure. An unfavorable outcome was present only if severe birth asphyxia (Apgar scores: 1-min,  $\leq 3$ ; 5-min,  $\leq 6$ ) or perinatal mortality occurred. Analysis by chi square and Student t test was used in comparing the data.

# Results

Eighty-two patients were examined between August and December, 1979. The mean maternal age, parity, gestational age, racial distribution, and frequency of

0002-9378/80/180210+03\$00.30/0 © 1980 The C. V. Mosby Co.

any antepartum complications are listed in Table I. Scanning for fetal motion was usually done once for each pregnancy, and often prior to intervention for some antepartum complication. Twenty-four pregnancies were complicated by prematurely ruptured amniotic membranes.

Table II compares the types of fetal motion viewed sonographically and perceived by the patient. The patient's subjective sensation registered 82% of all motions viewed sonographically. All combined motions of the fetal trunk and lower limbs observed sonographically were perceived by the patients and were described as strong movements (kicks, stretches, rollovers, balling-up). Clusters of independent, isolated motions of the fetal limbs were less frequent and were perceived less accurately (56% accuracy) in all patients as weak or "flutter" movements. Motion of the upper extremities was perceived only in association with strong motion of the lower limbs.

Each fetal movement perceived by the patient was visible on the ultrasound screen and involved motion of the lower limbs. The mean perceptible fetal motion during the 15-minute test period was significantly (p < 0.001) greater in pregnancies with ruptured amniotic membranes (9.2  $\pm$  1.8) than in pregnancies with intact membranes (4.2  $\pm$  0.6). The accuracy of perceptible fetal motion did not significantly (p < 0.05) vary with the presence or absence of ruptured amniotic membranes.

Maternal obesity, parity, gestational age, or Braxton-Hicks uterine contractions did not influence the patient's sensation of fetal activity. The localization of any perceived fetal movement by the patient was generally very accurate. No "hiccup" or strong diaphragmatic movements were present during the test period.

Fifty-five patients were delivered of infants within 5 days after the ultrasound procedure. The mean gestational age at delivery was  $37 \pm 4$  weeks. Only one fetus among the 45 who displayed strong movement (trunk with limb) had any significant neonatal complication; this fetus suffered from severe growth retardation and an encephalocele and died shortly after the induced vaginal delivery. Of the ten fetuses without visibly strong movement, five were perceived as being active later that day and subsequently were delivered without complication. The other five fetuses remained motionless that same day and had unfavorable neonatal outcomes related to hydrocephalus (3), severe Rh isoimmunization (1), and an occult prolapsed umbilical cord (1).

# Comment

The data from this relatively large number of patients substantiate the mother's reliability in perceiving

Table I. Patient population

Age Parity	$24.4 \pm 6.5$ years $1.0 \pm 0.4$
Gestational age	$34.4 \pm 4.4 \text{ weeks}$
Race distribution	86% white, 14% black
Antepartum course	No. of patients
No apparent complication	24 (29%)
Complication	58 (71%)
Prematurely ruptured amniotic membranes	24
Postdatism	8
Prior poor obstetric history	6
Diabetes mellitus	5
Hypertension	5
Suspected intrauterine growth re	e- <b>4</b>
Other	6

Table II. Accuracy of maternal perception of fetal

Tuboof	Fetal m	Accuracy	
Type of fetal movement	Perceived	Visualized	of patient perception (%)
Trunk and limb*	506	506	100
Isolated limb†	<u> 194</u>	349	<u>_56</u>
Total	700	855	82

<sup>\*</sup>Described as strong movements (kick, stretch, rollover, balling-up).

fetal activity, as reported by Sadovsky and associates,4 in Israel, and Gettinger and associates, in Great Britain. The variation in individual perception with the use of real-time ultrasonography was not so great in this study as that reported by Gettinger and associates. The patients were able to localize the various perceptible fetal movements and to differentiate between them.

This is the first known report to differentiate between strong (combined trunk and lower limbs) and weak (isolated limb) fetal movements. Visible fetal motion was characterized by means of the patient's terminology in describing perceived fetal activity.

Fetal motion after prematurely ruptured amniotic membranes has also not been described. The decreased intrauterine space was not found to be restrictive. Instead, fetal activity occurred more than twice as frequently, and the maternal perception of fetal motion was as accurate as that of patients with intact amniotic membranes. The monitoring of fetal motion is now being used to follow our expectantly managed pregnancies with prematurely ruptured amniotic membranes.

Our data support the findings of Manning and associates3 that a visibly active fetus is reassuring. A lack of visible motion of the fetal trunk with limbs may be ex-

<sup>†</sup>Described as weak or "flutter" movement.

plained by a fetal rest period, the patient's supine position, or true fetal distress. A fetus described by the patient as being inactive within that same day warrants the testing of fetal heart rate and repeat real-time ultrasonography.

# REFERENCES

- Gettinger, A., Roberts, A. B., and Campbell, S.: Comparison between subjective and ultrasound assessment of fetal movement, Br. Med. J. 2:88, 1978.
- Sadovsky, E., Yaffe, H., and Poleshuk, W.: Fetal movement monitoring in normal and pathologic pregnancy, Int. J. Gynaecol. Obstet. 12:75, 1974.
- 3. Manning, F., Platt, L., and Sipos, L.: Fetal movements in
- human pregnancies in the third trimester, Obstet. Gynecol. 54:699, 1979.
- Sadovsky, E., Mahler, Y., Poleshuk, W. Z., and Malkin, A.: Correlation between electromagnetic recording and maternal assessment of fetal movement, Lancet 1:1141, 1973.
- Rayburn, W. F., and McKean, H.: Maternal perception of fetal movement and perinatal outcome, Obstet. Gynecol. In press.

# Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January I, 1978. Therefore, all manuscripts must be accompanied by the following written statement, signed by one author: "The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C. V. Mosby Company in the event the work is published. The undersigned author warrants that the article is original, is not under consideration by another journal, and has not been previously published. I sign for and accept responsibility for releasing this material on behalf of any and all co-authors." Authors will be consulted, when possible, regarding republication of their material.

# Intrapartum fetal heart rate monitoring

# IV. Observations on elective and nonelective fetal heart rate monitoring

H. B. KREBS, M.D.

R. E. PETRES, M.D.

L. J. DUNN, M.D.

A. SEGRETI, PH.D.

Richmond, Virginia

Heart rate tracings and outcome in 919 electively and 1,077 nonelectively monitored fetuses were compared in order to investigate the value of elective surveillance of the fetal heart rate (FHR) in either group. A threefold higher perinatal mortality and a twofold higher number of low 5-minute Apgar scores were observed among patients with risk factors compared to electively monitored pregnancies. In the beginning of monitored labor, fetuses with risk factors exhibited a higher incidence of FHR patterns with low FHR variability than fetuses without risk factors. In the final phase of labor, FHR patterns indicative of hypoxia, i.e., late decelerations and severe and atypical variable decelerations, were found more often in the nonelective than in the elective group. Umbilical cord problems reflected by the occurrence of variable deceleration were responsible for the majority of low Apgar scores observed among electively monitored fetuses. The findings and their implications for FHR monitoring are discussed. (Am. J. Obstet. Gynecol. 138:213, 1980.)

SINCE Hon, in 1958,¹ first reported the usefulness of electronic evaluation of the fetal heart rate (FHR), monitors have become standard equipment in the majority of obstetric services in the United States today and play an important role in the intrapartum management of high-risk pregnancies. Although multiple indications for monitoring have evolved and are well accepted, the usefulness of intrapartum FHR monitoring for elective purposes is still controversial.² In the present study, FHR changes in fetuses with and without indications for monitoring were quantitated and related to fetal outcome in order to draw conclusions in regard to the value of FHR monitoring in either group.

From the Departments of Obstetrics and Gynecology and Biostatistics, Medical College of Virginia, Virginia Commonwealth University.

Received for publication January 23, 1980.

Revised March 18, 1980.

Accepted April 1, 1980.

Reprint requests: Hans-Bartold Krebs, M.D., Department of Obstetrics and Gynecology, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298.

## Material and methods

The study was performed in a retrospective manner and included 1,996 FHR tracings obtained from patients in labor during the time period of 1975 to June, 1977. The selected FHR tracings were obtained by internal FHR monitoring and were technically adequate to allow interpretation of FHR patterns mentioned below (Tables IIIA and IIIB). Only pregnancies of 34 weeks' gestation or more were included in the study. The time of monitoring exceeded 2 hours and included at least 30 minutes of the first stage of labor.

The first 30 minutes of FHR tracings obtained from patients immediately after admission to the labor and delivery unit and the last 30 minutes of FHR tracings prior to delivery were analyzed for baseline FHR, amplitude of oscillations, frequency of oscillation, accelerations, and decelerations. To each of these FHR patterns, 0 to 2 points were attributed according to a modified FHR Scoring System in a manner previously described. FHR patterns scoring less than 6 points were called "abnormal," 6 and 7 points "suspicious," and over 7 points "normal."

The patients were divided into two groups: those who had indications for monitoring according to the

Table I. Relationship between indication for monitoring, FHR score, and Apgar score

	N	Perinatal deaths	First 30 min FHR score <8	Last 30 min FHR score <8	5-min Apgar score <7
Nonelective					
Obstetric history factors					
Age >35 <16	83	0	5	26	2
Diabetes mellitus	35	1	3	19	3
Chronic hypertension	28	1	2	8	3
Cardiac disease	4	0	0	i	Ī
Rh sensitization	3	0	0	1	0
Sickle cell disease	2	0	0	0	0
Prenatal and intrapartum factors					
Anemia (Hb $< 10$ gm per dl)	39	0	3	14	2
Preeclampsia	199	4	12	74	16
Eclampsia	5	1	1	2	2
Suspected postterm (>42 weeks)	82	1	6	28	4
Polyhydramnios	22	2	4	13	4
Clinical evidence of intrauterine growth retardation	31	2	3	12	3
Vaginal bleeding, partial placental abruption	14	1.	1	5	2
Premature rupture of membranes	336	2	22	112	11
Meconium-stained fluid	284	7	42	125	22
Abnormal fetal heart tones by auscultation	31	0	18	. 8	1
Pyelonephritis	4	0	0	1	0
Amnionitis	15	0	1	. 5	1
Abnormal labor not requiring oxytocin augmentation	292	2	19	. 82	9
Induction of labor	313	4	14	96	21
Augmentation of labor	147	· 1	8	. 39	6
Premature labor*	57	1.	4	19 .	3
Conduction anesthesia	47	0	4	14	2
Total nonelectively monitored patients	1,077	16	91	373	62
Elective	-				
Total electively monitored patients	919 ′	. 5	65	254	24

<sup>\*</sup>Pregnancies of less than 34 weeks were excluded from the study.

**Table II.** Nonelective and elective fetal monitoring. Patient characteristics

	Elective		Nonel		
	Mean	SD	Mean	SD	P*
Patient age	21.8	5.4	21.9	5.3	>0.05
Parity	0.73	1.41	0.72	1.36	>0.05
Time monitored (hr)	5.30	3.94	6.96	4.87	< 0.001

<sup>\*</sup>t test.

**Table IIIA.** Nonelective and elective FHR monitoring. Abnormal FHR patterns, first 30 min

	Elective		Nonelective		
First 30 min	n	% of total	n	% of total	P*
Tachycardia	33	3.6	32	3.0	>0.05
Bradycardia	21	2.3	28	2.5	>0.05
Oscillatory amplitude (<6 beats/min)	180	19.6	257	23.9	< 0.05
Oscillatory frequency (≤6 oscillations/min)	13	1.4	48	4.5	< 0.001
Accelerations (<5/30 min)	249	27.1	288	26.7	>0.05
Early decelerations	50	5.4	43	4.0	>0.05
Late decelerations	12	1.3	19	1.8	>0.05
Variable decelerations	133	14.5	106	9.8	< 0.005

<sup>\*</sup>Chi-square test.

**Table IIIB.** Nonelective and elective FHR monitoring. Abnormal FHR patterns, last 30 min

		•			
	Ele	ctive	None	lective	
Last 30 min	n	% of total	n	% of total	P*
Tachycardia	50	5.4	59	5.5	>0.05
Bradycardia	161	17.5	201	18.7	>0.05
Oscillatory amplitude (<6 beats/min)	224	24.4	327	30.4	< 0.005
Oscillatory frequency (≤6 oscillations/min)	27	2.9	66	6.1	< 0.005
Accelerations (<5/30 min)	367	40.0	425	39.5	>0.05
Early decelerations	156	17.0	109	15.7	>0.05
Late decelerations	31	3.5	58	5.3	< 0.05
Variable decelerations					
Total	476	51.8	512	47.5	>0.05
Mild and moderate	371	40.4	341	31.6	< 0.001
Severe and atypical	105	11.4	171	15.8	< 0.05

<sup>\*</sup>Chi-square test.

American College of Obstetricians and Gynecologists Technical Bulletin from January, 1977<sup>5</sup> (nonelective or indicated or risk group) and those who did not (elective group). Pertinent data from the patient's records were computerized. Analysis for limits of confidence was carried out by t test and chi-square test corrected for continuity.

	n	Variable d	lecelerations	One-min Ap	ogar score <7	Five-min Ap	bgar score <7
		Total	% of n	Total	% of n	Total	% of n
Elective group Nonelective group	919 1,077	476 512	51.3 47.5	82* 147*	8.9 13.6	17 30	1.8 2.8

Table IV. Nonelective and elective FHR monitoring. Variable decelerations in last 30 min of monitored labor

#### Results

The elective FHR monitoring group consisted of 919 patients (46.0%) and the nonelective group, of 1,077 patients (54.0%). Of the patients listed in Table I, 677 had more than one and as many as five indications for FHR monitoring. Patients with preeclampsia, premature rupture of membranes, and meconium-stained amniotic fluid comprised the largest portion of patients with risk factors. In none of the patients listed under "Induction of labor" was labor stimulated for elective purposes.

A threefold higher perinatal mortality and a significantly higher number of low 5-minute Apgar scores (p < 0.001) were observed among risk patients compared to electively monitored pregnancies (Table I). Although there was no difference in age and parity, patients in the risk group were monitored significantly longer (p < 0.001) than those monitored electively (Table II).

In the first 30 minutes of FHR monitoring, low oscillatory amplitude and frequency occurred significantly more often in the nonelectively monitored group than in the electively monitored group (p < 0.05). The reverse was true for the occurrence of variable decelerations (Table IIIA).

FHR patterns in the last 30 minutes also showed a higher incidence of low variability among risk patients (p < 0.05); in addition, late decelerations were significantly increased in the nonelective group compared to the elective one (p < 0.05). The overall occurrence of variable decelerations did not differ significantly between the two groups; however, when subdivided into groups of mild and moderate as opposed to severe and atypical variable decelerations, a shift toward more severe FHR abnormalities among nonelectively monitored fetuses became evident: mild and moderate variable decelerations prevailed among electively monitored patients, whereas severe and atypical variable decelerations were more common among patients with risk factors (p < 0.05, Table IIIB). This particular distribution largely explains the higher number of low Apgar scores associated with variable decelerations in the risk group as compared to the nonrisk group (Table IV, p < 0.01).

Table V. Nonelective and elective FHR monitoring. Comparison of FHR tracing scores

	Elective		Nonelective			
	Mean	SD	Mean	SD	P*	
FHR score of first 30 min FHR score of last 30 min					>0.05 <0.05	

<sup>\*</sup>t test.

The mean FHR scores in the first 30 minutes of FHR monitoring were not significantly different in the two groups (p > 0.05). However, FHR patterns during the last 30 minutes of monitoring received lower mean FHR scores in the nonelective group than in the elective group (p < 0.05, Table V).

Abnormal FHR patterns scoring 7 or less were quite rare during the first 30 minutes of monitoring and occurred in 7% among electively and in 8% among nonelectively monitored pregnancies. The difference is not statistically significant (p > 0.05, Table VIA). In the last 30 minutes of monitored labor, however, abnormal FHR patterns were observed more frequently: 29% of electively and 34% of nonelectively monitored patients received FHR scores of 7 or less. The difference is statistically significant (p < 0.05, Table VIB).

Comparison of the frequency of low Apgar scores reveals a higher incidence of low 1-minute and 5minute Apgar scores in the risk group than in the nonrisk group. Such a difference is also observed in several FHR scoring categories of both groups (p < 0.05, Tables VIA and VIB). In other words, a low FHR score (7 or less) was prognostically more unfavorable for patients with risk factors than for patients without risk factors. Similarly, normal FHR patterns (FHR score of 8 or more) provided better assurance of good fetal outcome in terms of Apgar scores in patients without risk factors than in those with risk factors. Therefore, the sensitivity, i.e., correct identification of adverse fetal outcome, was higher in the nonelective group; the specificity, i.e., identification of good fetal outcome, was higher in the elective group (Tables VIIA and VIIB).

Abnormal FHR patterns were chief indications for operative intervention in 72 cases (7.8%) of electively

<sup>\*</sup>P < 0.01 chi-square test.

**Table VIA.** Nonelective and elective FHR monitoring. Relationship between low Apgar score and FHR score, first 30 min of monitored labor

First 30 min					One-min Ap	gar score <7	Five-min Ap	ogar score <
	N %	% of totai	n	%	n	%		
Elective group, total	919	100.0	146ª	15.9	24 <sup>c</sup>	2.6		
FHR score <6	5	0.5	5	100.0	3	60.0		
6 and 7	60	6.5	29	48.3	9	15.0		
>7	854	93.0	112 <sup>b</sup>	13.1	12 <sup>d</sup>	1.4		
Nonelective group; total	1,077	100.0	258ª	23.9	62 <sup>c</sup>	5.7		
FHR score <6	18	1:6	18	100.0	13	72.2		
6 and 7	73	6.8	36	49.3	12	16.4		
>7	986	91.6	$204^{b}$	20.6	37 <sup>d</sup>	3.8		

Statistically significant differences (P < 0.05) are indicated by pa red symbols a-a through d-d. Chi-square test.

Table VIB. Nonelective and elective FHR monitoring. Relationship between low Apgar score and FHR score, last 30 min of monitored labor

	N % of total	One-min Apgar score <7		Five-min Apgar score <		
Last 30 min		% of total	n	%	n	%
Elective group, total	919	100.0	146e	15.9	24 <sup>8</sup>	2.6
FHR score <6	23	2.5	20	87.0	11	47.8
6 and 7	241	26.2	70	27.9	10	4.0
>7	655	71.3	56 <sup>f</sup>	8.7	3 <sup>h</sup>	0.5
Nonelective group, total	1,077	100.0	- 258e	23.9	`62 <sup>g</sup>	5.7
FHR score <6	50	4.7	45	90.0	24	48.0
6 and 7	313	29.0	110	36.3	22	7.3
>7	714	66.3	103 <sup>f</sup>	14.2	16 <sup>h</sup>	2.2

Statistically significant differences (P < 0.05) are indicated by paired symbols e-e through h-h. Chi-square test.

and in 114 cases (10.6%) of nonelectively monitored pregnancies. The difference was statistically significant (p < 0.05). Emergency cesarean sections were employed more often in the risk group (53 cases, 4.9%) than in the elective group (25 cases, 2.7%, p < 0.025). Emergency forceps delivery accounted for the remainder of operative interventions and was used in 61 cases of risk pregnancies (5.7%) and in 47 cases (5.1%) of electively monitored pregnancies. The difference here was not statistically significant (p > 0.05). There was a total of 28 cesarean sections in the elective group (3.0%) and 293 (27%) in the nonelective group. Most indications in the latter group (188 cases) were for abnormalities of labor.

# Comment

A compromised fetal respiratory situation is commonly reflected by FHR abnormalities. For this reason, a high incidence of abnormal FHR patterns is likely to be found among pregnancies complicated by risk factors predisposing to impairment of maternal-fetal gas exchange. Certain conditions, such as chronic hypertension, diabetes mellitus, and preeclampsia, are known to cause vascular changes that limit transplacental oxygen transfer. The fetus may also suffer from

hypoxia secondary to maternal anemia or heart disease. Moreover, the use of oxytocin for the induction or augmentation of labor has been implicated in detrimental effects on the fetus during episodes of hyperstimulation. All of these conditions and many more are commonly accepted indications for intrapartum FHR monitoring.

The present study confirms that pregnancies with certain recognizable risk factors are frequently associated with abnormal FHR patterns and result in unfavorable fetal outcome more often than pregnancies without such risk factors. The incidence of low 1-minute and 5-minute Apgar scores was significantly higher in the nonelective FHR monitoring group than in the elective group (Tables VIA and VIB); perinatal mortality was observed in 16 pregnancies (1.4%) with risk factors but in only five pregnancies (0.5%) without risk factors (Table I).

The difference in fetal outcome was reflected by a higher incidence of abnormal FHR patterns in the group of nonelectively monitored pregnancies. In the last 30 minutes of monitoring, the risk group received a significantly lower mean FHR score than the nonrisk group and yielded a higher number of FHR scores less than 7 (Tables V, VIA, and VIB). The FHR tracings

Table VIIA. Elective and nonelective FHR monitoring. Sensitivity, specificity, false positive, false negative rates, first 30 min of monitored labor

First 30 min	Elective group	Nonelective group
Sensitivity	12/24 = 50.0(%)	37/62 = 59.7(%)
Specificity	842/854 = 98.6	949/986 = 96.2
False positive FHR score < 6	2/5 = 40.0	5/18 = 27.8
FHR score 6	51/60 = 85.0	61/73 = 83.6
False negative	12/854 = 1.4	37/986 = 3.8

Sensitivity = correct identification of adverse outcome (5min Apgar score <7). Specificity = correct identification of good outcome (5-min Apgar score ≥7). False positive = low FHR score (<8) associated with good outcome. False negative = normal FHR score (>7) associated with adverse outcome.

differed significantly in the incidence of low FHR variability, as well as late and variable decelerations (Tables IIIA and IIIB).

FHR variability is strongly influenced by certain drugs, such as morphine compounds, phenothiazines, diazepoxide, and magnesium sulfate.<sup>7</sup> Although both the electively and the nonelectively monitored patients received meperidine and hydroxyzine, only patients in the high-risk group, i.e., those with preeclampsia and eclampsia, received magnesium sulfate. Therefore, the prognostic significance of lower FHR variability in the group with risk factors may be questioned. An important subpopulation of nonelectively monitored patients, however, who did not receive magnesium sulfate, consisted of pregnancies complicated by meconium-stained amniotic fluid. This group has been shown to exhibit a significant increase in abnormal variability patterns and a decreased number of accelerations, a finding which was interpreted as indicative of reduced fetal reserve.8 Many fetuses with other risk factors in this study exhibited low FHR variability already at the initiation of monitoring before medications were administered (Table IIIA).

The frequent occurrence of late decelerations in the last 30 minutes of monitored labor and the high number of low Apgar scores may well be the expression of poor tolerance of labor, which was already foreshadjowed by low FHR variability in many cases.

The occurrence of hypoxia as evidenced by late de-

celerations depends not only on certain intrinsic placental and fetal factors but also on the duration and the strength of labor. Since pregnancies with risk factors were monitored significantly longer than pregnancies without risk factors, the difference in fetal outcome may be attributed to a difference in the length of labor. However, many of the high-risk patients were in-house

Table VIIB. Elective and nonelective FHR monitoring. Sensitivity, specificity, false positive, false negative rates, last 30 min of monitored labor

Last 30 min	Elective group	Nonelective group
Sensitivity	21/24 = 87.5(%)	46/62 = 74.2(%)
Specificity	652/655 = 99.5	698/714 = 97.8
False positive	•	
FHR score <6	12/23 = 52.2	26/50 = 52.0
FHR score 6	231/241 = 95.9	291/313 = 93.0
False negative	3/655 = 0.5	16/714 = 2.2

Sensitivity = correct identification of adverse outcome (5min Apgar score <7). Specificity = correct identification of good outcome (5 min Apgar score ≥7). False positive = low FHR score (<8) associated with good outcome. False negative = normal FHR score (>7) associated with adverse outcome.

patients who were placed on the monitor as soon as labor started, whereas electively monitored patients were usually in good labor at the time of admission to the hospital. Therefore, the duration of monitoring was not identical with the time of labor.

The higher incidence of well-established labor at the time of initiation of FHR monitoring in the electively monitored group also accounts for the difference in variable decelerations between the two groups of patients: in the first 30 minutes of monitoring, variable decelerations occurred significantly more often in the electively monitored group than in the nonelective group, whereas no such difference was found in the last 30 minutes of FHR monitoring (Tables IIIA and IIIB). Variable decelerations were the most frequent abnormal FHR patterns encountered in our series and merit special consideration. As opposed to late decelerations, variable decelerations do not primarily reflect fetal hypoxia but, rather, hemodynamic changes secondary to sequential compression of the umbilical vein and arteries during uterine contractions.9

A hypoxic component may supervene if the duration of the interruption of the fetal blood supply surpasses a certain limit.10 The threshold is likely to be low in borderline compensated fetuses on the verge of hypoxia secondary to a compromised maternal-fetal gas exchange. Certainly, many patients with risk factors, such as preeclampsia, maternal diabetes, or chronic hypertension, fall into this category. Therefore, it is not surprising that we observed significantly more severe and atypical variable decelerations with a concomitant increase in low Apgar scores in the pregnancies with risk factors than in those which were monitored electively (Table IV).

A normal FHR tracing is generally associated with good fetal outcome11; individual abnormal FHR pat-

terns, on the other hand, correlate poorly with low Apgar scores or fetal acidosis. 4 The fetal status is better reflected by multiple FHR changes at the same time which may be assessed separately and quantitated by a FHR scoring system. 12 Poor fetal prognosis correlates directly with the height of the FHR score. In the present study, FHR tracings were allocated to one of three prognostic categories according to the FHR score. The outcome for fetuses with and without risk factors was then compared within each scoring category and revealed that electively monitored fetuses received higher Apgar scores than nonelectively monitored fetuses with quantitatively identical FHR changes (Tables VIA and VIB). It appears that certain risk factors have a particular impact on fetal prognosis. For example, fetuses with indications for monitoring were significantly more often delivered by cesarean section than those without risk factors. For reasons which will be discussed in a subsequent report, fetuses with the same FHR score received lower Apgar scores when delivered by cesarean section than when delivered vaginally. Similarly, fetuses with meconium-stained amniotic fluid received lower Apgar scores than those without, in spite of quantitatively identical FHR changes.8

Electively monitored fetuses have little danger from hypoxia secondary to uteroplacental insufficiency. However, they are exposed to umbilical cord problems just as frequently as fetuses with indications for monitoring: 72% of low 5-minute Apgar scores of fetuses without risk factors were associated with variable decelerations which are known to reflect compression of the umbilical cord. Labor itself imposes a significant risk upon any fetus, thus demanding the utmost attention to this critical phase of life. Electronic surveillance of the FHR is, above all other means, suitable because of its high sensitivity and specificity.

Over 50% of low 5-minute Appar scores were correctly identified by abnormal FHR patterns at the time of initiation of monitoring. Just prior to delivery, FHR patterns predicted approximately 80% of adverse and 99% of good fetal outcomes. Nineteen of the fetuses who suffered perinatal mortality (90%) exhibited abnormal FHR tracings. Retrospective analysis of the intrapartum and postpartum management of neonates who died suggests that the outcome in at least five of the risk patients and two of the electively monitored patients may have been more fortunate if abnormal FHR patterns indicative of fetal distress had prompted earlier operative intervention. Similarly, approximately 50% of electively and nonelectively monitored fetuses with low 5-minute Apgar scores might have performed better if the FHR abnormality had been recognized earlier and decisive action taken sooner.

A major problem associated with FHR monitoring is the high false positive rate, i.e., occurrence of abnormal FHR patterns not associated with clinically obvious fetal distress. Abnormal FHR scores (5 or less) commonly represent severe FHR abnormalities, consisting of late or severe variable decelerations, low variability, and absence of sporadic accelerations. We called this pattern a "decompensated distress pattern" and found that it was associated with 89% of low 1-minute and 48% of low 5-minute Apgar scores. 12 The false positive rates of 11% and 48%, respectively, are tolerable. Unfortunately, over 85% of abnormal FHR patterns obtained a "suspicious" FHR score (6 and 7 points) indicative of a "compensated distress pattern." These fetuses frequently exhibited low 1-minute Apgar scores (32%) but infrequently low 5-minute Appar scores (6%). The false positive rates of 68% and 94% are so high that operative intervention based on a suspicious FHR pattern cannot be recommended. Instead, attempts to improve the FHR pattern by positional change of the mother, administration of oxygen, careful manipulation of the fetus, or inhibition of uterine activity should be made. Low FHR variability and lack of sporadic accelerations should not be considered to be prognostically unfavorable until attempts to arouse the fetus have been made. A patient with a suspicious FHR score should be delivered by the most expeditious route if the FHR pattern worsens inspite of the application of the conservative measures outlined above. We think that FHR monitoring applied in this manner provides a most useful basis for intrapartum management of fetuses with and without risk factors.

# Conclusions

- 1. Fetuses with risk factors do not tolerate the stress of labor well. They often exhibit signs of a compromised respiratory situation and suffer from a high perinatal morbidity and mortality. Abnormal FHR patterns indicative of low fetal reserve (decreased FHR variability) and hypoxia (late decelerations; severe or atypical variable decelerations) occur more frequently in the risk than in the nonrisk group.
- 2. Fetal outcome in the risk group is also influenced by the risk factors themselves, which may modify intrapartum and postpartum management: electively monitored fetuses received higher Apgar scores than nonelectively monitored fetuses with quantitatively identical FHR changes.
- 3. Fetuses without risk factors have the same chance of suffering from umbilical cord problems as do fetuses with risk factors. Cord problems are frequent, unpredictable, and responsible for the majority of low Apgar scores observed among electively monitored fetuses.

Variable decelerations give early and reliable warnings of funicular complications. This is a strong argument for routine monitoring of every patient in labor.

4. FHR monitoring is a very sensitive and specific method for identification of fetal stress situations. A

high incidence of abnormal FHR tracings associated with good fetal outcome requires evaluation of the FHR pattern in the light of response to intrauterine resuscitative methods.

#### REFERÈNCES

- Hon, E. H.: The electronic evaluation of the fetal heart rate. Preliminary report, Am. J. Obstet. Gynecol. 75:1215, 1958.
- Lee, W. K., and Baggish, M.: The effect of unselected intrapartum fetal monitoring, Obstet. Gynecol. 47:516, 1976.
- 3. Shenker, L., Post, R. C., and Seiler, J. S.: Routine electronic monitoring of fetal heart rate and uterine activity during labor, Obstet. Gynecol. 46:185, 1975.
- Krebs, H. B., Petres, R. E., Dunn, L. J., Jordaan, H. V. F., and Segreti, A.: Intrapartum fetal heart rate monitoring. I. Classification and prognosis of fetal heart rate patterns, Am. J. Obstet. Gynecol. 133:762, 1979.
- American College of Obstetricians and Gynecologists Technical Bulletin: Intrapartum fetal monitoring, Chicago, 1977, American College of Obstetricians and Gynecologists, nr. 44.
- Kubli, F. W., Hon, E. H., Khazin, A. F., and Takemura, H.: Observations on heart rate and pH in the human fetus during labor, Am. J. OBSTET. GYNECOL. 104:1190, 1969
- 7. Petrie, R. H., Yeh, S., Murata, Y., Paul, R. H., et al.: The

- effects of drugs on fetal heart rate variability, Am. J. Obster. Gynecol. 130:294, 1978.
- 8. Krebs, H. B., Petres, R. E., Dunn, L. J., Jordaan, H. V. F., and Segreti, A.: Intrapartum fetal heart rate monitoring. III. Association of meconium with abnormal fetal heart rate patterns, Am. J. Obstet. Gynecol. 137:936, 1980.
- James, L. S., Yeh, M.-N., Morishima, H. O., Daniel, S. S., et al.: Umbilical vein occlusion and transient acceleration of the fetal heart rate, Am. J. Obstet. Gynecol. 126:276, 1976.
- Caldeyro-Barcia, R., Mendez-Bauer, C., Poseiro, J. J., and Pose, S. V.: Fetal monitoring in labor, in Wallace, H. M., Gold, E. M., and Lis, E. F., editors: Maternal and Child Health Practices, Springfield, Illinois, 1973, Charles C Thomas, Publisher, pp. 332-394.
- Thomas, Publisher, pp. 332-394.

  11. Schifrin, B. S., and Dame, L.: Fetal heart rate patterns. Prediction of Apgar scores, J. A. M. A. 219:1322, 1972.
- Prediction of Apgar scores, J. A. M. A. 219:1322, 1972.

  12. Krebs, H. B., Petres, R. E., Dunn, L. J., Jordaan, H. V. F., and Segreti, A.: Intrapartum fetal heart rate monitoring. II. Multifactorial analysis of intrapartum fetal heart rate tracings, Am. J. Obstet. Gynecol. 133:773, 1979.

# Re-evaluation of birth weights at high altitude

Study of babies born to mothers living at an altitude of 3,100 meters

ERNEST K. COTTON, M.D. MAHLON HIESTAND, M.D. GEORGE E. PHILBIN, M.D. MICHAEL SIMMONS, M.D.

Denver and Leadville, Colorado

Babies born at altitudes above 2,700 meters have been reported to be below normal birth weight and small for gestational age (SGA). In a study of a specific community (Leadville, Colorado, altitude 3,100 meters) over a period of 14 months (ending November, 1978), 215 newborn infants were found to be appropriate for gestational age (AGA), with the entire group having a mean birth weight (3.16 kilograms) similar to that of newborn infants in Denver, Colorado (3.12 kilograms). This study from a community with a stable population indicates that babies born at high altitude are AGA. The increased morbidity which does occur for these babies is not due to SGA factors. (AM. J. OBSTET. GYNECOL. 138:220, 1980.)

BIRTH WEIGHT has been reported to be lower for babies born at high altitude. 1, 2 McCullough and associates3 confirmed this observation and indicated that these babies were also small for gestational age (SGA). Their data were obtained from Colorado birth certificates of babies born between 2.744 and 3.100 meters and between the years 1969 and 1973. Lahiri and associates,4 when studying the ventilatory response to hypoxia of babies born at 3,850 meters (Puno, Peru), also indicated that babies born at high altitude were SGA. In all of these reports, problems exist: (1) questionable lack of consistency in reporting weights with proper gestational age; (2) variations in the management of pregnancy, such as adhering to the practice of limiting maternal gain in weight to under 9.1 kilograms (20 pounds); (3) the possibility of chronic undernutri-

> From the Department of Pediatrics, University of Colorado School of Medicine, Denver, and St. Vincent's Hospital, Leadville.

This study was supported by Grant No. HL-15430 from the National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Received for publication October 10, 1979.

Revised March 17, 1980.

Accepted March 27, 1980.

Reprint requests: Ernest K. Cotton, M.D., Department of Pediatrics, University of Colorado School of Medicine, 4200 East Ninth Ave., Denver, Colorado 80262.

tion in women before the onset of pregnancy. Since morbidity and mortality may be increased for babies born at high altitude, and since SGA babies do carry a higher risk factor than those appropriate for gestational age (AGA),<sup>5</sup> an accurate determination of birth weight and gestational age is necessary. This report concerns a select population living at an altitude of 3,100 meters. Our clinical impression was that babies born at that altitude were not smaller than babies born at lower elevations. The findings verified the clinical impression that babies born at 3,100 meters are appropriate in weight for gestational age.

#### Method of study

Maternal population. All the mothers who were included in this study had lived in Leadville, Colorado, for more than 2 years. These mothers did not travel below 3,100 meters for more than 10 days during their pregnancy. The population was made up of 25% Mexican-Americans and 75% Caucasians. Both parents had completed a minimum of 10 years of education, with 82% of the mothers and 89% of the fathers having had 12 years or more of education.

Management of pregnancy and delivery. The pregnancies were consistently managed by one of four family practitioners who had their offices in Leadville. The women were not malnourished prior to pregnancy, and the average gain in weight ± standard deviation

**Table I.** Distribution of 215 babies born in Leadville, according to gestational age, and comparison of gestational age determined by physical examination to gestational age by last menstrual period

Gestational age by last menstrual period (wk)	No. of babies	Gestational age by physical examination (wk)
. 33	2	33—1 baby 34—1 baby
34	2	34—1 baby 40—1 baby
35	4	35—3 babies
36	6	39—I baby 36—E babies
37	10	40—1 baby 36—2 babies
38	13	37—& babies 37—& babies
		38—6 babies 39—5 babies
39	61	42—1 baby 36—1 baby
		37—1 baby 39—58 babies
	0.5	40—I baby
40	86	38—1 baby 39—8 babies
	٠	40—75 babies 41—1 baby
. 41	21	42—1 babý 36—1 baby
***	21	39—1 baby
		40—6 babies 41—13 babies
42	10	39—2 babies 40—6 babies
		42— baby 43— baby
		45— Dady

was  $9.64 \pm 0.80$  kilograms (or 19.5 to 23 pounds). All mothers who had lived in Leadville for 2 years or more were included in the study; 15 had a gain in weight below 9.1 kilograms, and 21 had a gain in weight above 11.3 kilograms.

**Data analysis.** Each baby was placed into a group according to gestational age as determined by the mother's last menstrual period. The mean and standard deviation were determined for weight and length in each group. The weight data were plotted on the Colorado Intrauterine Growth Chart.<sup>7</sup>

#### Results

Two hundred and fifteen babies were delivered during a 14-month period ending November, 1978. During this period, age at birth fell between 33 and 42 weeks' gestation. In general, the gestational age determined by the last menstrual period corresponded to that determined at birth by physical examination

Table II. Mean and one standard deviation (1 SD) of weights and lengths of 215 babies as those measurements relate to gestational age determined by last menstrual period

Gestational age (wk)	Weight (hg) (Mean ± 1 SD)	Length (cm) (Mean ± 1 SD)
33	1.95 ± 0.21	42.55 ± 6.29
34	$2.55 \pm 0.46$	$45.10 \pm 2.69$
35	$2.23 \pm 0.57$	$45.18 \pm 4.51$
36	$2.41 \pm 0.59$	$44.45 \pm 4.11$
37	$2.59 \pm 0.57$	$45.10 \pm 2.41$
38	$2.85 \pm 0.21$	$47.18 \pm 2.20$
39	$2.97 \pm 0.42$	$47.93 \pm 2.75$
40	$3.22 \pm 0.42$	$48.88 \pm 2.57$
41	$3.32 \pm 0.46$	$49.70 \pm 3.21$
42	$3.18 \pm 0.44$	$49.85 \pm 3.08$

(Table I). The mean weight for the entire group was 3.18 kilograms ± 2.16 (one standard deviation). Table II gives the mean and standard deviation (SD) for the weights and lengths of the babies for each gestational age (as determined by last menstrual period). The weights are plotted as their means and SD on the growth chart. Fig. 1 indicates where these babies fit for weight at each gestational age range. The mean weight for each age group fell between the twenty-fifth and seventy-fifth percentiles, but three groups (35, 36, 37) were slightly below the twenty-fifth percentile. No baby fell outside of the nineteenth or ninetieth percentile of the growth chart.

#### Comment

During the period of 1969 to 1973, McCullough and associates3 calculated that the mean birth weight for babies born at high altitude was 2.92 kilograms compared to 3.16 kilograms for babies born in Denver. During our 14-month study that ended in November, 1978, the mean birth weight was 3.18 kilograms, which is comparable to the 3.16 kilograms recorded for babies in Denver. Fig. 1 and Table II show that the babies in Leadville were also AGA and not SGA as found by McCullough and associates.3 Since McCullough and associates took their data from the birth certificates of Colorado babies, their report encompassed the entire mountain area of the state and did not focus on one community. Multiple factors aside from high altitude could alter the birth weight, but a study of a single community would eliminate some variables.

Leadville is a large mining community comprised of 10,000 persons living at 3,100 meters. The Leadville hospital is the highest in North America. Economically, the mining industry is very stable, and has not resulted in any fluctuations in population. Per capita income for this county (Lake County) ranks second highest in the

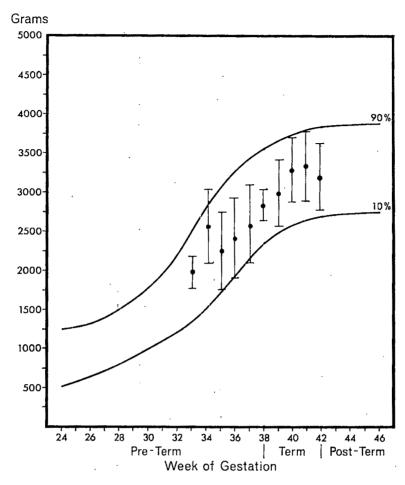


Fig. 1. Mean birth weight  $\pm 1$  SD as plotted for week of gestation as determined by last menstrual period. Gestational graph is from Lubchenco and associates.<sup>7</sup>

state. Prenatal care was consistent, and no unusual dietary restrictions were imposed. The mother's gain in weight was not limited to 9.1 kilograms (20 pounds) or less. Labor was not induced unless cesarean section was indicated. It is possible that the low birth weight<sup>6</sup> may have resulted from prior obstetric practice which prevailed in the mountain communities and was not related to altitude. Our analysis of the birth weights, lengths, and gestational ages of neonates from a very stable population living at 3,100 meters indicates that

babies born of mothers who have lived at 3,100 meters for at least 2 years have the same weights and the same gestational ages as those of babies born in Denver and at sea level. This is the first study which indicates that infants born at altitude are not of lower birth weight than those born at sea level, but it must be recognized that a selected population was studied.

With the elimination of the risk of a low birth weight, other factors which may increase morbidity and mortality for babies born at altitude can be evaluated.

#### REFERENCES

- Lichty, J. A., Ting, R. Y., Bruns, P. D., and Dyar, E.: Studies of babies born at altitude, Am. J. Dis. Child. 93:666, 1957.
- 2. Kruger, F., and Arias-Stella, J.: The placenta and the newborn at high altitudes, Am. J. Obstet. Gynecol. 106:586, 1970.
- 3. McCullough, R. E., Reeves, J. T., and Liljegren, R. L.: Fetal growth retardation and increased infant mortality at high altitude, Arch. Environ. Health 37:36, 1977.
- 4. Lahiri, S., Brady, J. S., Motoyama, E. K., and Velasquez,
- T. M.: Regulation of breathing in newborns at high altitude, J. Appl. Physiol. 44:673, 1978.
- Lubchenco, L. O.: High Risk Infant, Philadelphia, 1976,
   W. B. Saunders Co.
- Nutrition and Fetal Development. In Winick, M., editor: Current Concepts in Nutrition, New York, 1974, John Wiley and Sons, Inc., vol. 2, chap. 6.
   Lubchenco, L. O., Hansman, C., and Boyd, E.: In-
- Lubchenco, L. O., Hansman, C., and Boyd, E.: Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 26 to 42 weeks, Pediatrics 37:403, 1966.

# CURRENT INVESTIGATION

This section offers prompt first announcement of new observations or discoveries. Articles should be limited to 1,500 words and six references. Illustrations or additional references require a proportionate reduction in total words.

# An alternative to antepartum fetal heart rate testing

WILLIAM RAYBURN, M.D.
FREDERICK ZUSPAN, M.D.
MARY ELLEN MOTLEY, L.P.N.
MARCIA DONALDSON, R.N.
Lexington, Kentucky, and Columbus, Ohio

The high-risk pregnancies of 203 patients were prospectively studied to test the hypothesis that the maternal perception of fetal movement is as useful as antepartum fetal heart rate testing (AFHRT) in assessing fetal welfare. Evidence for an active fetus (186 cases, 92%) was usually followed by a normal AFHRT result (320/330 results, 97%). Furthermore, a favorable perinatal outcome was equally predicted by an active fetus (168/186 cases, 90%) and a normal AFHRT result (173/190 cases, 91%). Evidence for an inactive fetus was less sensitive but not significantly different from an abnormal AFHRT in predicting an unfavorable perinatal outcome (10/17 cases versus 11/13 cases, p > 0.05). However, an abnormal AFHRT result coincident with fetal inactivity was highly predictive of an unfavorable neonatal outcome in nine of 10 cases. In conclusion, the data reveal that a record of fetal activity by the compliant patient is a reliable a ternative to AFHRT for the initial screening of fetal well-being. (AM. J. OBSTET. GYNECOL. 138:223, 1980.)

ANTEPARTUM FETAL HEART rate testing (AFHRT), which includes nonstress testing (NST) and contraction stress testing (CST), has gained popularity in assessing fetal well-being. However, the time required to satisfactorily perform or repeat each test, the difficulty in interpretation, and the overall cost-effectiveness can be definite limitations. An alternate method to initially

From the Departments of Obstetrics and Gynecology, University of Kentucky Medical Center, and The Ohio State University Hospital and Clinics.

Reprint requests: William Rayburn, M.D., Department of Obstetrics and Gynecology, The Ohio State University Hospital, 410 W. 10th Ave., Columbus, Ohio 43210.

screen fetal welfare may overcome such restrictions and improve the usefulness of AFHRT.

At this institution, many pregnant patients with antepartum complications have been instructed to record perceived fetal motion for a minimum 1-hour rest period each day. Our general impression has been that an active fetus is reassuring and will be associated with a normal AFHRT result and an eventual favorable perinatal outcome. Prior studies involving sensitive electromagnetic devices and real-time ultrasonography have shown the maternal perception of fetal movement to be reliable. The purposes of this investigation were to determine the predictability of fetal movement pat-

**Table I.** Patients who had antepartum complications and counted fetal movements

	Patients			
Antepartum complication	No.	%		
Postdates	85	41.9		
Pregnancy-induced hypertension	28	13.8		
Diabetes mellitus	21	10.3		
Chronic hypertension	14	6.9		
Prior stillbirth	12'	5.9		
Suspected fetal growth delay	11	5.4		
Third-trimester bleeding	6	3.0		
Rh isoimmunization	. 6	3.0		
Other	20	9.9		
Total	203	100		

**Table II.** Fetal movement pattern and subsequent AFHRT result

		Subsequent AFHRT result					
Engl					mal	Abno	rmal
Fetal movement pattern	No of tests	No.	%	No.	%		
Active	330	320	97	10	3		
Inactive	19	9	44	10	56		
Total	349	329	94	20	6		

terns with subsequent AFHRT results to compare recent fetal movement patterns with AFHRT results in predicting the subsequent course of the fetus during labor and after delivery.

# Material and methods

This prospective investigation was undertaken during a 16-month period at the University of Kentucky Medical Center (September, 1978, to April, 1979) and at The Ohio State University Hospital and Clinics (July, 1979, to February, 1980). Any patient who was cared for by the authors and whose antepartum course was complicated was asked to participate after the thirty-third week of gestation, when intervention for fetal interest seemed plausible. The maternal age, race, parity, primary antepartum complication, and gestational age at delivery were recorded. To avoid confusion, any pregnancy complicated by prematurely ruptured amniotic membranes or by multiple gestation was excluded.

The patient was told to record any perceived fetal movement (except hiccups) during at least one convenient hour each day. She was encouraged to lie on her left side to improve uteroplacental circulation. Patients were told to contact these investigators when a concern about a lack of fetal movement occurred. Charts given

to the patient to record perceived fetal movements were returned at each clinic visit, during admission for delivery, or in the mail after postpartum discharge.

Clinical judgment was required in differentiating between an active and an inactive fetal movement pattern. Two consecutive days of apparent fetal inactivity and classification in the lower 5% of all cases from all weeks were considered prerequisites for a fetus to be classified as inactive. The fetal movement charts were reviewed to determine a critical value for a number of fetal movements per hour, such that when applied for any two consecutive days across all patients, the result would give 5%. The value determined for an inactive fetal movement pattern was three or less movements per hour for two consecutive days. A fetus was considered active if four or more movements were perceived for each convenient hour of daily counting.

The fetal movement pattern of each pregnancy was compared to each subsequent AFHRT result. NST was routinely done initially and interpreted by two or more physicians as being either reactive, nonreactive, or unsatisfactory6 without prior knowledge of the fetal activity pattern. For the NST result to be reactive, two or more adequate accelerations of the fetal heart rate baseline during the initial observation period or upon fundal palpation were necessary.6, 7 A reactive NST result was usually repeated weekly.7 A repeat nonreactive NST result required CST, which was interpreted as positive, suspicious, or negative. A normal AFHRT result was defined as a reactive NST or a negative CST. An abnormal AFHRT result was a nonreactive NST (only if a CST was contraindicated) or a suspicious or positive CST.

Within the week prior to delivery, the result of the most recent AFHRT (normal or abnormal) and the daily fetal movement pattern (active or inactive) were independently compared to the subsequent fetal outcome during labor and after delivery. The perinatal outcome (favorable or unfavorable) was determined by two or more physicians. The outcome was classified as unfavorable if one or more of the following was present: (1) perinatal mortality, (2) abnormal fetal heart rate tracing during the first stage of labor (persistent severe variable decelerations, repetitive late decelerations, prolonged unexplainable loss of beat-to-beat variability), (3) combined Appar scores of ≤6 at 1 minute and at 5 minutes, (4) severe fetal growth retardation (lower fifth percentile of birth weight for gestational age), (5) major fetal anomaly, or (6) prolonged neonatal hospitalization (>5 days) for complications other than social or prematurity reasons.

The data from both institutions were compiled and

analyzed with Student's t test and chi-square test analysis. A p value greater than 0.05 was considered not significant.

#### Results

Of the 203 qualifying patients, 86 were from the University of Kentucky and 117 from The Ohio State University. These two groups of patients did not vary significantly (p > 0.05) in maternal age (26  $\pm$  5 years, range 16 to 39 years), race (73% white, 27% black), parity (38% primiparous), and gestational age (41  $\pm$  3 weeks, range 34 to 45 weeks). Primary antepartum complications principally involved postdatism (>42 weeks), hypertension, and diabetes mellitus (Table I). The majority of the patients were routinely examined in our outpatient clinics and did not require antepartum hospitalization (166 of 203 cases, 82%)

Table II compares the prior fetal movement pattern with 349 subsequent AFHRT results. The majority of conditions involved an active fetus and a subsequent normal AFHRT result (320 of 330 tests, 97%). Evidence for an inactive fetus was frequently followed initially by a nonreactive NST result (14 of 19 tests) and required repeat NST or CST. The 10 abnormal AFHRT results with prior evidence of an active fetus involved nonreactive NSTs with a contraindication to CST (3), suspicious CSTs (4), and positive CSTs (3).

Table III compares fetal movement patterns with AFHRT results in predicting the perinatal outcome. A favorable perinatal outcome was present in the majority of pregnancies (175 of 203 cases, 86%), and the predictive value of an active fetal movement pattern (168 of 186 cases, 90%) was not significantly different (p > 0.05) from the predictive value of a normal AFHRT result (173 of 190 cases, 91%). An unfavorable perinatal outcome following such reassuring results was not more commonly associated with a particular antepartum complication (postdates, hypertension, diabetes mellitus) but was more related to intrapartum complications (umbilical cord accidents, traumatic delivery, inappropriate analgesia or anesthesia), major congenital anomalies (anencephaly, hydrocephalus, Ebstein's anomaly), neonatal respiratory distress (meconium aspiration, inappropriate intubation, transient tachypnea, group B streptococcal pneumonia), and fetal alcohol syndrome. Two cases were found in which the unfavorable perinatal outcome was preceded by evidence of an active fetus but an abnormal AFHRT result. Late decelerations on intrapartum fetal moni-•toring in the case complicated by pregnancy-induced hypertension was related to a partial abruptio placentae. The other pregnancy was complicated by diabe-

Table III. Comparison of fetal movement pattern, recent AFHRT result, and subsequent perinatal outcome

		Perinatal outcome			
		Favorable		Un- favorable	
Test result	est result No. of patients No. %		No.	%	
Active fetus:					
Normal AFHRT	183	167	91	16	9*
Abnormal AFHRT	. 3 .	1	33	2	66
Inactive fetus:		4	_		
Normal AFHRT	7	6	86	1	14
Abnormal AFHRT	10	1	10	9	90
Total	203	175	86	28	14

<sup>\*</sup>Involved intrapartum complications (umbilical cord accidents, traumatic delivery), major fetal anomalies, neonatal respiratory distress, and fetal alcohol syndrome.

tes mellitus with renal involvement, and the fetus was mildly growth retarded and mildly hydrocephalic.

An inactive fetal movement pattern was less sensitive than an abnormal AFHRT result in predicting an unfavorable perinatal outcome (10 of 17 cases of 59% versus 11 of 13 cases or 86%), but this difference was not significant (p > 0.05). An inactive fetus with an abnormal AFHRT result was very predictive of an unfavorable perinatal outcome in nine of 10 cases. Conditions associated with an unfavorable perinatal outcome involved hydrocephalus (2), severe Rh isoimmunization (2), maternal sepsis and acidosis (2), fetal peritonitis, severe fetal growth retardation in a known drug addict, and a nuchal cord accident.

# Comment

Data from this large number of high-risk pregnancies substantiate prior preliminary reports that a pregnancy with an active fetus will be followed by a normal AFHRT result.1, 3 This was especially true when a nonreactive NST result was followed by reactive NST or negative CST results. Timor-Tritsch and associates8 have shown that fetal heart rate acceleration (>10 bpm above the baseline) has been observed in 91% to 100% of fetal movements (especially rolling or stretching motions).

This is the first known report to show that an active fetus as described by daily fetal movement counting is as predictive as a normal AFHRT result in forecasting a favorable perinatal outcome. An inactive fetus was less sensitive in determining fetal distress than an abnormal AFHRT result, and the effort and expense to undertake AFHRT are recommended.

This noninvasive technique has many positive fea-

tures. The patient can become more involved in assessing her child's well-being prior to birth and is reassured with an active fetus. Rest while reclining on her left side for 1 hour or more each day is stressed and should improve uteroplacental perfusion. Readily available information outside the clinic setting is gained on a daily rather than a semiweekly basis. Fetal heart rate testing would be more cost-effective if indicated for complicated pregnancies only when an inactive fetus is recorded or when fetal movement counting has not been performed.

False positive or reassuring results with the fetal movement technique were infrequent (18 of 186 cases). Reasons to explain this disparity were the same as for fetal heart rate testing and involved intrapartum or neonatal complications beyond the technique's testing capabilities.

The technique of fetal movement counting was generally well accepted. Ideally, high-risk pregnancies should be followed closely by the same physician(s) who can communicate well with the patient. New charts were given to the patient at each clinic visit, and returned charts were placed on the antepartum record. Patient anxiety was infrequent, and concern expressed to the physician was uncommon. This counting technique is now being used as early as the twenty-eighth week of gestation.

## REFERENCES

- Rayburn, W. F., and McKean, H. E.: Maternal perception of fetal movement and perinatal outcome, Obstet. Gynecol. In press.
- Sadovsky, E., Mahler, Y., Palishuk, W. Z., and Malken, A.: Correlation between electromagnetic recording and maternal assessment of fetal movement, Lancet 1:1141, 1973.
- Manning, F. A., Platt, L. D., and Sipos, L.: Fetal movements in human pregnancies in the third trimester, Obstet. Gynecol. 54:699, 1979.
- Rayburn, W. F.: Clinical significance of perceptible fetal motion. Am. J. OBSTET. GYNECOL. 138:210, 1980.
- Gettinger, A., Roberts, A. D., and Campbell, S.: Comparison between subjective and ultrasound assessment of fetal movement, Br. Med. J. 2:88, 1978.
- Keegan, K. A., and Paul, R. H.: Antepartum fetal heart rate testing. IV. The nonstress test as a primary approach, Am. J. Obstet. Gynecol. 136:75, 1980.
- 7. Rayburn, W. F., Greene, J., and Donaldson, M.: Nonstress testing and perinatal outcome, J. Reprod. Med. In press.
- 8. Timor-Trisch, I. E., Dierker, L. J., Zador, I., Hertz, R., and Rosen, M.: Fetal movements associated with fetal heart rate accelerations and decelerations, Am. J. Obstet. Gynecol. 131:276, 1978.

#### Erratum

In the January 15, 1980, issue of the Journal, in the article, "Amniotic fluid lipids in sickle cell disease," by Das and Foster, on page 212, in the third sentence under the "Results" heading, the excitation and emission maxima values were reversed. The sentence should read, "Lipid extracts from amniotic fluid of sickle cell patients showed fluorescence excitation and emission maxima at the 345 nm and 450 nm regions, respectively.



# NATAFORT-TO HELP ASSURE A NUTRITIONALLY COMPLETE PREGNANCY

#### **PARKE-DAVIS**

Div of Warner-Lambert Co Morris Plains, NJ 07950 USA PD-JA-0043-1-P (1-80) © 1980 Warner-Lambert Company



# convenience of Gantanol°

sulfamethoxazole/Roche



Convenient, economical first-line therapy

# Gantanol' NS

sulfamethoxazole/Roche 2 tablets initially, then only 1 tablet B.I.D.

# Only one tablet B.I.D.

Only Gantanol DS offers the convenience of a *single* sulfonamide tablet on a *b.i.d.* schedule. With fewer daily doses, patients are more likely to comply with your prescribed regimen.

# Effective first-line therapy

In a controlled study of 406 patients involving *E. coli* and the other most common causative organisms of acute nonobstructed cystitis, nearly 9 out of 10 patients achieved clear cultures with Gantanol. (Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.)

Gantanol is contraindicated in sulfonamide hypersensitivity, pregnancy, lactation, and infants under two months of age. During therapy instruct patients to maintain adequate fluid intake; perform frequent CBC's and urinalyses with careful microscopic examination.

# **Economical**

Gantanol therapy, which often costs less than other frequently prescribed urinary antibacterials, becomes even more economical for your patients when you select Gantanol DS (double strength) tablets.



Gantanol

sulfamethoxazole/Roche

4 tablets initially, then only 2 tablets B.I.D.

# Only 1 tablet B.I.D.

# Gantanol® DS sulfamethoxazole/Roche

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Acute, recurrent or chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Aerobacter*, staphylococcus, *Proteus mirabilis* and, less frequently, *Proteus vulgaris*), in the absence of obstructive uropathy or foreign bodies. Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections. Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

**Contraindications:** Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: Blood dyscrasias (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypopro-thrombinemia and methemoglobinemia); allergic reactions (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reac tions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); gastrointestinal reactions (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); CNS reactions (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); miscellaneous reactions (drug fever, chills, toxic nephrosis with oliguria and anuria periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypo-glycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis). *Usual adult dosage*: 2 Gm (2 DS tabs or 4 tabs or 4 teasp.) initially, then 1 Gm b.i.d. or t.i.d. depending on severity of infection.

depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs b.i.d.

Maximum dose should not exceed 75 mg/kg/24 hrs.

Supplied: DS (double strength) Tablets, 1 Gm sulfamethoxazole; Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazoler.

ROCHE Division of Hoffmann-La Roche Inc.

Nutley, New Jersey 07110

# CLINICAL BIOSTATISTICS:

# here's why you'll benefit from this book

- authoritative articles from <u>Clinical Pharmacology and</u> Therapeutics
- clear and easy-to-read explanations of essential statistical concepts
- provocative insights into the common sense and science behind statistical data

## CLINICAL BIOSTATISTICS

This unique book critically examines the entire field of clinical biostatistics. It presents a series of original articles that first appeared over a five year period in *Clinical Pharmacology and Therapeutics*. Widespread reader acclaim and the timeliness of the subject prompted publication of the essays into convenient book form.

The essays are logically arranged into 29 chapters and organized into five major sections, each preceded by brief commentary written especially for the book. You'll find informative discussions on the diverse statistical techniques used in medical practice and research; research and design problems; presentation of data; and methods of data analysis. Dr. Feinstein has reorganized his original articles to provide you with a completely current guide to the biostatistics used in both clinical and investigative situations. He also offers valuable insights into topics either totally neglected or inadequately covered in conventional texts. Throughout, discussions are written in lively prose style, which makes the subject both interesting to read and easy-to-understand. Why not benefit from Dr. Feinstein's expert guidance firsthand-order your copy of CLINICAL BIOSTATISTICS today!

By Alvan R. Feinstein, M.D., 1977, 468 pages plus FM I-XIV, 6-7/8" x 10", 10 illustrations. Price, \$21.50

# **ORDER BY PHONE!**

Call toll free (800) 325-4177 ext. 10. In Missouri call collect—(314) 872-8370 ext. 10 during normal business hours.

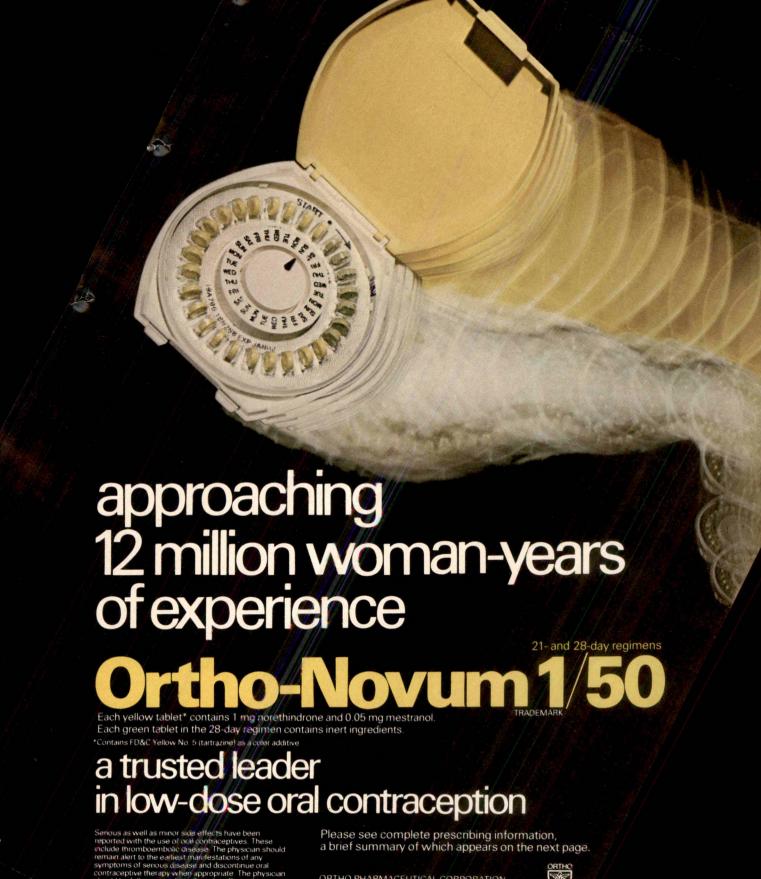
A80794

Price effective in U.S.A. only.



THE C V MOSBY COMPANY

11830 WESTLINE INDUSTRIAL DRIVE
ST LOUIS MISSOURI 63141



IMPORTANT NOTE—This information is a BRIEF SUMMARY of the complete prescribing information provided with the product therefore should not be used as the basis for prescribing the product. This summary was prepared by deleting from complete practining information certain tart, tables, and references. The physician should be thoroughly familiar with complete prescribing information and patient information before prescribing the product.

INDICATION: CONTRACEPTION. The pregnancy rate in women using conventional combination oral contraceptives (containing 35 mcg or more of ethinyl estradiol or 50 mcg or more of mestranol) is generally reported as less than one pregnancy per 100 woman-years of uses. Slightly higher rates (somewhat more than one pregnancy per 100 woman-years of use) are reported for some combination products containing 35 mcg or less of ethinyl estradiol, and rates on the order of the pregnancies per 100 woman-years are reported for the progestogen-only oral contraceptives. Table 1 gives ranges of pregnancy rates reported in the literature for other means of contraception. The efficacy of these means of contraception (except the IUD) depends upon the degree of adherence to the method.

Table 1: Pregnancies Per 100 Women-Years. IUD, less than 1-6. Diaphragm with spermicidal product (creams or jeillies), 2-20. Condom, 3-36. Aerosol foams, 2-29. Jeilles and creams, 4-36. Periodic abstinence (rhythm) all types, less than 1-47. 1. Calendar method. M-47. 2. Temperature method, 1-20; 3. Temperature method—intercourse only in postiovulatory phase, less than 1-7, 4. Mucus method, 1-25, No contraception, 60-80. DOSE-RELATED Risks 0F THROMBOCHBOLISM FROM DATE (CNITACEPTIVES: Two studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. For this reason, it is prudent and in keeping with good principles of therapeutics to minimise exposure to estrogen. The oral contraceptive product prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance it recommended that new acceptors of oral contraceptive sets attarted on preparations containing 0.5 mg or less of estrogen. CONTRALEPTIONS: Oral contraceptives should not be used in women with any of the following conditions: 1. Thrombophilebits or thromboembolic disorders: 2. A past history of deep vein thrombophelbitis or

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking [15 or more cigarettes per day] and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke. The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism. stroke, myocardial infarction, hepatic adenoma, galibladder disease, hyperiension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

stroke, myccrrilar infarction, hepatic adenoma, galibladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. THROMBOEMBOLLC DISGROERS AND OTHER VASCULAR PROBLEMS. An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Four principal studies in Great Britain and three in the United States have demonstrated an increased risk of fatal and nonitatal venous thromboembolism and stroke onto hemorrhagic and thromboembolic. These studies estimate that users of oral contraceptives are 4 to 11 times more likely than nonusers to develop these diseases without evident cause. Overall excess mortality due to pulmonary embolism stroke is on the order of 1.0 to 3.5 deaths annually per 100,000 users and increases with age. CERBANSEQULAR DISGROERS: In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, twas estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than in nonusers.

#WOCARDAL INFARCTION: An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported confirming a previously suspected association. These studies, conducted in the United Kingdom, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, thyperension, thypercholesterolemia, obesity, diabetes, history of preclamptic toxemia), the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor. The annual excess case rate (increased risk) of myocardial infarction (fatal and nonfatal) in oral contraceptive users was estimated to be approximately 7 cases per 100,000 women users in the 40-44 age group; in terms of relative risk, it has been estimated that oral contracept however, an independent risk factor for these events. **ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES:** A large prospective study carried out in the United Kingdom estimated the mortality rate per 100,000 women year from diseases of the circulatory system for users and nonusers of oral contraceptives according to age, smoking habits, and duration of use. The overall excess death rate annually from circulatory diseases for oral contraceptive users was estimated to be 20 per 100,000 (ages 15-346-35/100,000; ages 35-449-340/100,000), the risk being concentrated in older women, in those with a long duration of use, and in cigarette smokers. It was not possible, however, to examine the interrelationships of age, smoking, and duration of use, not to compare the effects of continuous versus intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for five or more years, all of these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for five or more years are available, it is not possible to assess the magnitude of the relative risk for this younger age group. Another study published at the same time confirms a previously reported increase of mortality in pill users from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. The estimates of risk of death for each method include the combined isk of the contraceptive methods. associated with various methods of contraception. The estimates of risk of death for each method include the combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease in the case of oral contraceptives plus this kathibitudable to pregnancy or abortion in the event of method failure. This latter risk varies with the effectiveness of the contraceptive method. The findings of this analysis are shown in Figure 1 below. The study concluded that the mortality associated with all methods of birth control is low and below that associated with childborth, with the exception of oral contraceptives in women over 40 who smoke. (The rates given for pill only/smokers for each age group are for smokers a class. For "heavy" smokers [more than 15 cigarettes a day], about 50 percent.) The mortality associated with oral contraceptive use in nonsmoker over 40 is higher than with any other method of contraception in that age group. The lowest mortality is associated with the condom or diaphragm backed up by early abortion. The risk of thromboembolic and thrombotic disease associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preclamptic toxemia and especially by cigarette smoking. The risk of myocardial infarction in oral contraceptive users is substantially increased in women age 40 and over, especially those with other risk factors. Based on the data currently available, the following chart gives a gross estimate of the risk of death from circulatory disorders associated with the use of oral contraceptives:

OMORING HADITO AND UTHEN PHEDIOLOGING	COMDITIONS-I	HON HOOD	UINILU	WITH DOL OF OHNE CONTINUE TIVES
Age	Below 30	30-39	40+	
Heavy smokers	С	В	A	A-Use associated with very high risk.
Light smokers	D	C	В	B-Use associated with high risk.
Nonsmokers (no predisposing conditions)	D	C,D	C	C-Use associated with moderate risk.
Nonsmokers (other predisposing conditions)	C	C.B	B.A	D-Use associated with low risk.

Nonsnokers (other predisposing conditions)... C C.B. B.A D—Use associated with intolerater iss. Nonsnokers (other predisposing conditions)... C C.B. B.A D—Use associated with intolerater iss. Nonsnokers (e.g., thrombophlebits, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, refund thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A four- to six-fold increased risk of postsurgery thromboembolic complications has been reported in contraceptive users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization. 2. OCULAR LESIONS. There have been reports of neuro-ocular lesions such as optic neurities or retinal thrombosis associated with the use of oral contraceptives. Discontinue oral contraceptive medication if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilidedema; or retinal vascular lesions and institute appropriate diagnostic and therapeutic measures. 3. CARCINOMA. Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in oral contraceptives, have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs. In humans, three case control studies have reported an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium (e.g., irregular bleeding at the time oral contraceptives were first of contraceptives. The contraceptive is not not not propestogen-only oral contraceptives. Several studies have found no increases in breast canc

Figure 1. Estimated annual number of deaths associated with control of fertility and no control per 100,000 nonsterile

	15-19	20-24	25-29	30-34	35-39	40-44
No method	5.5	5.2	7.1	14.0	19.3	21.9
Abortion only	2.3	2.5	2.5	5.2	9.8	6.6
Pill only-nonsmokers	1.3	1.4	1.4	2.2	4.5	3.1
Pill only-smokers	1.5	1.6	1.6	10.8	13.4	58.9
IUDs only	1.1	1.2	1.2	1.4	1.6	1.4
Traditional contraception only	1.1	1.4	1.9	3.7	4.7	4.0
Traditional contraception and abortion	0.3	0.4	0.4	0.8	1.4	0.8

observed while receiving oral contraceptives. An increase in triglycerides and total phospholipids has been observed in patients receiving oral contraceptives. The clinical significance of this finding remains to be defined. 8 ELEVER BLOOD PRESSURE. An increase in blood pressure has been reported in patients receiving oral contraceptives. In some women hypertension may occur within a few months of beginning oral contraceptive use. In the first year of use, the prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. The prevalence in the first year, Age is also strongly correlated with the development of hypertension in oral contraceptive users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure when given oral contraceptives. Hypertension that develops as a result of taking oral contraceptives usually returns to normal after discontinuing the drug. 9. HEADACHE. The onset or exacerbation of migraine or development of haedache of a new pattern which is recurrent, persistent, or severe, requires discontinuing of a contraceptives and evaluation of the cause. 10. BLEEDING IRREGULARITIES. Breakthrough bleeding, as in all cases or irregular bleeding from the vagina, nonfunctional causes should be bome in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy of pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done in mind. In undiagnosed persistent or recurrent pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only in necessar may also occur in women without previous irregularities. 11 ECTOPIC PREGNANCY: Ectopic as well as intrauterine pregannoy may occur in contraceptive failures. 12 EBREAST FEEDING. Oral contraceptives given in the postpartum period may
interfere with lactation. There may be a decrease in the quantity and quality of the breast milk. Furthermore, a small
raction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The
effects, if any, on the breast-led child have not been determined. If feasible, the use of oral contraceptives should be
deterred until the infant has been weaned, PREAUTIONS: General: 1. A compiler medical and family history, should be taken
prior to the initiation of oral contraceptives. The pretreatment and periodic physical examination being performed. 2 Under the influence of estrogen-progestogen preparations, presextising uterine isomory,
tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another physical
examination being performed. 2 Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size 3. Patients with a history of psychic depression should be carefully observed and the drug
discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether
the symptom is drug-related. A Oral contraceptives may cause some degree of fluid retention. They should be prescribed
with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convolvable disorders, migraries syndrowine, asthma, or cordiace or renal insufficiency. S. Patients with a past instruy
of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving past shirts, or journal prescribed to the patients of the pr

# Articles to appear in early issues

# Time-lapse study of normal human trophoblast in vitro

Judith Lueck, B.S., and Silvio Aladjem, M.D. Chicago and Maywood, Illinois

# Technical failures in tubal ring sterilization: Incidence, perceived reasons, outcome, and risk factors

I-cheng Chi, M.D., Dr.P.H., Stephen D. Mumford, Dr.P.H., and Leonard E. Laufe, M.D. Research Triangle Park, North Carolina

# The double uterus associated with an obstructed hemivagina and ipsilateral renal agenesis

John A. Rock, M.D., and Howard W. Jones, Jr., M.D. Baltimore, Maryland

# Stable prolactin level after enhanced estradiol production following dehydroepiandrosterone sulfate

A. Kauppila, M.D., and O. Ylikorkala, M.D.

Oulu, Finland

# Evidence for a human ovarian progesterone receptor

Barry R. Jacobs, M.D., Susan Suchocki, and Roy G. Smith, Ph.D. Houston, Texas

# Postpartum lymphocytic thyroiditis in American women: A spectrum of thyroid dysfunction

Henry G. Fein, M.D., Joel M. Goldman, M.D., and Bruce D. Weintraub, M.D. Bethesda, Maryland

# Ultrasound measurement of fetal limb bones

John T. Queenan, Gregory D. O'Brien, and Stuart Campbell London, England

# Possible acceleration of neurological maturation following high-risk pregnancy

Claudine Amiel-Tison
Paris, France

# Maternal and fetal immune responses to human trophoblast antigens

Pamela V. Taylor Leeds, England

# In serious intra-abdominal and pelvic infections...

# The clinical importance and virulence of Bacteroides fragilis

# Clinical importance of B. fragilis

Bacteroides fragilis is a major anaerobic pathogen in abdominal and pelvic infections. Both aerobes and anaerobes are involved in the majority of serious intraabdominal and female pelvic infections. Therefore, early antimicrobial therapy against both pathogens should be considered.

Two studies have confirmed the value of including *Cleocin Phosphate*™ (clindamycin phosphate injection, NF) as part of the therapy for serious intra-abdominal and pelvic infection.

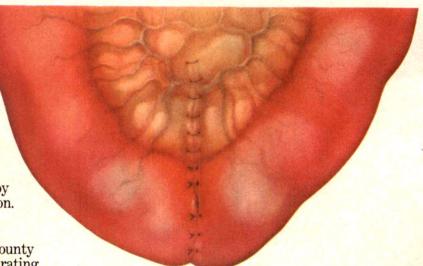
Penetrating abdominal wounds

In a prospective, randomized study at Cook County Hospital, Chicago, 100 patients who had penetrating abdominal wounds, with spillage of bowel contents, were given kanamycin (0.5 gram ql2h) and either clindamycin (600 mg q6h) or cephalothin (3 grams q6h). The clindamycin/kanamycin-treated group showed significantly fewer episodes of septicemia or intra-abdominal sepsis. The higher complication rate in the cephalothin/kanamycin group was the result of infections due to anaerobic bacteria alone or a mixture of aerobes and anaerobes (see Table 1).

Table 1	Cephalothin/ Kanamycin	Clindamycin/ Kanamycin
Number of patients	52	48
Septic complications Septicemia	7	2
Intra-abdominal abscesses  Total complications	14	5

Postcesarean endomyometritis

In a prospective, randomized study at the University of Southern California Medical Center among



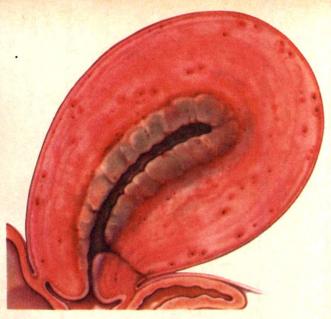
200 women who developed endomyometritis following cesarean section, the clinical response was more favorable in those receiving clindamycin (600 mg q6h) and gentamicin (60-80 mg q8h) than in those receiving penicillin (5 million units q6h) and gentamicin (60-80 mg q8h) (see Table 2).<sup>2</sup>

Table 2	Penicillin/ Gentamicin	Clindamycin/ Gentamicin
Number of patients	100	100
No response—third		
antibiotic required	29	5
Serious complications*	4	0
Mean duration of hospital stay (days)	8.7	7.4
Mean febrile degree hours	110	81
Mean febrile degree hours in	E. Mary	Part Hell
eight patients who developed	256.4	73.4
Bacteroides bacteremia	(n = 6)	(n = 2)

<sup>\*1</sup> patient with pelvic abscess, 1 with wound evisceration, and 2 with septic thrombophlebitis.

Adapted from Ledger et al.2

The foregoing studies suggest that early treatment with *Cleocin Phosphate* in combination with an aminoglycoside is effective therapy in these serious infections and can prevent progression to more complicated and disseminated infection.



# Virulence of B. fragilis

As clinical studies have shown, antibiotics active against *B. fragilis* must be instituted early in the course of therapy for serious pelvic and abdominal infection to prevent complications due to this organism.

Research is currently being conducted to better define the virulence of *B. fragilis*.

Specific antigenic marker

Investigators at the Harvard Medical School have identified a capsular polysaccharide on the outer membrane of *B. fragilis*. In an experimental model, an antibody response to this antigen was associated with *B. fragilis* infection. The clinical significance of this antibody-antigen relationship is unknown.



Electron micrograph of B. fragilis stained by standard techniques (×120,000). A capsular polysaccharide has been identified on the outer membrane (arrow). A subsequent clinical study has shown that in the acute phase of pelvic inflammatory disease, women from whom *B. fragilis* was cultured after culdocentesis had a more significant change in antibody titer to the polysaccharide antigen than did women from whom *B. fragilis* was not isolated.

These data suggest that *B. fragilis* may play a significant role in acute pelvic inflammatory disease and may be involved early in the infectious process.

Antibiotic susceptibility

Cleocin Phosphate has maintained an excellent record of in vitro activity against B. fragilis.

If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued (see WARNING box). A summary of prescribing information for *Cleocin Phosphate*—used in the treatment of serious infections due to anaerobic pathogens—can be found on the following page.

For serious anaerobic infections...

# Cleocin Phosphate

(clindamycin phosphate injection, NF)

STERILE SOLUTION—FOR INTRAMUSCULAR AND INTRAVENOUS USE

# Cleocin Phosphate™

(clindamycin phosphate injection, NF)
STERILE SOLUTION—FOR INTRAMUSCULAR AND INTRAVENOUS USE

#### WARNING

Clindamycin therapy has been associated with severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less-toxic antimicrobial agents are inappropriate, as described in the INDICATIONS section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. Studies indicate a toxin(s) produced by Clostridia is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro. See WARNINGS section. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large-bowel endoscopy has been recommended

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains: clindamycin phosphate

When necessary, pH adjusted with NaOH and/or HCl.

**Indications:** Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less-toxic alternatives (eg, erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis, and lung abscess; serious skin and soft-tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft-tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft-tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

**Contraindications:** History of hypersensitivity to clindamycin or lincomycin.

Warnings: See WARNING box. Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro. Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte, and protein supplementation as indicated. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin in vitro. Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Nursing Mothers: Clindamycin has been reported to appear in breast milk in the range of 0.7 to 3.8 mcg/ml.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREAT-MENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

**Precautions:** Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high-dose therapy.

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeasts. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: Gastrointestinal: Abdominal pain, nausea, vomiting, and diarrhea. (See WARNING box.) Hypersensitivity Reactions: Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. Liver: Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. Hematopoietic: Neutropenia, eosinophilia, agranulocytosis, and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made. Local Reactions: Pain, induration, and sterile abscess have been reported after intramuscular injection, and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters. Musculoskeletal: Rare instances of polyarthritis have been reported.

**How Supplied:** Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin. Ampoules of 2 and 4 ml.

Caution: Federal law prohibits dispensing without prescription.

MED B-7-S

References: 1. Thadepalli H, Gorbach SL, Broido PW, Norsen J, Nyhus L: Abdominal trauma, anaerobes, and antibiotics. *Surg Gynecol Obstet* 137:270-276, 1973. 2. DiZerega G, Yonekura L, Roy S, Nakamura RM, Ledger WJ: A comparison of clindamycin-gentamicin and penicillin-gentamicin in the treatment of postcesarean section endomyometritis. *Am J Obstet Gynecol* 134:238-242, 1979.

The Upjohn Company, Kalamazoo, Michigan 49001

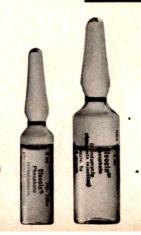
Upjohn

For serious anaerobic infections...

# Cleocin Phosphate

(clindamycin phosphate injection, NF)

STERILE SOLUTION—FOR INTRAMUSCULAR AND INTRAVENOUS USE



# COMMUNICATIONS IN BRIEF

This section is suitable for reporting results of therapeutic trials, descriptions of new procedures or instruments, and case reports which illustrate a principle. Reports should be limited to seven hundred words and two references. Use of an illustration or table requires a proportionate reduction in total words.

# Significance of fetal and neonatal sinusoidal heart rate pattern: Further clinical observations in Rh incompatibility

JOHN P. ELLIOTT, M.D., MAJOR, MC, USA HOUCHANG D. MODANLOU, M.D. DANIEL F. O'KEEFFE, M.D. ROGER K. FREEMAN, M.D.

Department of Maternal-Fetal Medicine, Women's Hospital and Earl and Loraine Miller Children's Hospital, Long Beach Memorial Hospital, Long Beach, California, and the Departments of Obstetrics and Gynecology and Pediatrics, University of California (Irvine), Orange, California

SINUSOIDAL FETAL HEART RATE (FHR) patterns have been observed in a number of different clinical situations. This pattern has been observed in cases of Rh isoimmunization with severe fetal compromise and fetal anemia secondary to massive fetomaternal transfusion. Sinusoidal FHR patterns have also been observed in severely asphyxiated fetuses as a premorbid phenomenon. In most of these previously reported cases the fetuses either died shortly after the onset of the sinusoidal pattern or were very severely compromised upon intervention.

Rh isoimmunized pregnancies are usually managed by analysis of the optical density at 450 m $\mu$  (OD<sub>450</sub>) of the amniotic fluid, serial ultrasound examinations for placental changes or fetal ascites and FHR monitoring. Reports in the literature estimate that serial OD<sub>450</sub> measurements are 95% accurate in predicting the severity

The opinions or assertions contained herein are the private views of the authors and are not to be considered official or as reflecting the views of the Department of the Army or the Department of Defense.

Reprint requests: John P. Elliott, M.D., Women's Hospital, 2801 Atlantic Ave., Long Beach, California 90801.

of fetal erythroblastosis and only 2% to 3% inaccurate to the point of being life-threatening. FHR monitoring has also detected fetal distress in Rh-sensitized fetuses. The purpose of this report is to describe a case where the combined use of these surveillance techniques facilitated detection of a severely affected neonate.

J. V., a 47-year-old woman, gravida 5, para 3, abortions 1, stillbirths 1, had a last menstrual period on February 3, 1978, giving an estimated date of confinement of October 18, 1978. Her reproductive history included a delivery in 1964 of a viable 8 pound, 1 ounce term male infant. In 1967, she was delivered of another male infant, weighing 8 pounds, at term. In 1973, she had a spontaneous abortion, and a curettage was performed. The fourth pregnancy, in 1976, resulted in a stillborn fetus at 36 weeks. She was Rh sensitized in the last pregnancy and had four amniocenteses, but the baby died in utero. The autopsy findings were consistent with hydrops fetalis. She had type A, Rh-negative blood and her husband was type A, homozygous Rh (D) positive. She had never received Rhogam. The first two babies were unaffected. Amniocentesis for genetic purposes was done at 16 weeks in this pregnancy and revealed a 46,XX karyotype and a normal level of alpha fetoprotein. Serial amniocenteses starting at 23 weeks' gestation were performed. The value of the ΔOD<sub>450</sub> was steadily decreasing in a reassuring fashion with the last value being 0.035 at 35 weeks' gestation (Fig. 1) and with a lecithin/sphingomyelin ratio of 1.0/1. The placenta was posterior and all amniocenteses were done under ultrasonic direction with no bloody taps encountered. No evidence of placental thickening, fetal ascites, or fetal edema was noted on any of the sonograms. Following the last amniocentesis (at 35 weeks) fetal surveillance was initiated by nonstress testing twice a week; the next tap was to be done at 37 to 38 weeks. Three reactive nonstress tests preceded a minimally reactive test (Fig. 2, Panel B) at 361/2 weeks' gestation. This test was repeated 2 days later when the patient noted an absence of fetal movement, at which time a sinusoidal FHR pattern was observed (Fig. 2, Panel C). Because of the usual ominous nature of the sinusoidal pattern in Rh-sensitized pregnancies, an immediate cesarean section was performed. The female infant weighed 3,000 gm, was pale, and had Apgar scores of 5,

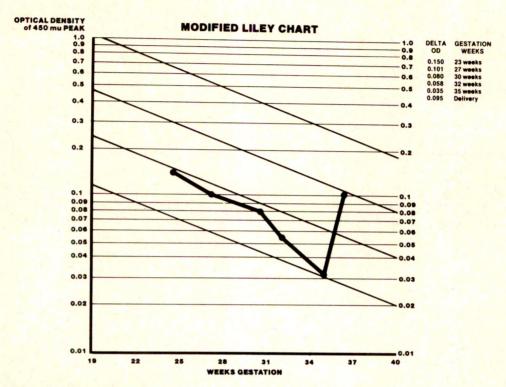


Fig. 1. Modified Liley graph depicting the fall in  $\Delta OD_{450}$  values until 35 weeks' gestation. Note the dramatic rise to 0.095 in amniotic fluid sampled at cesarean section.

7, and 9 at 1, 5, and 10 minutes, respectively. The  $\Delta OD_{450}$  of the amniotic fluid at the cesarean section was 0.095. A Kleihauer-Betke test of the mother's blood showed no fetal red blood cells. Cord blood hemoglobin was 5.7 gm/100 ml; hematocrit was 18.4%; and bilirubin was 10.6 mg/100 ml, with a strongly positive direct Coombs test.

Prior to delivery 2 U of sedimented type O, Rh-negative blood was matched with mother's serum in preparation for the infant's management. The infant was kept on 35% to 40% oxygen from birth while an umbilical arterial catheter was inserted for continuous monitoring of blood pressure and for exchange transfusions. Immediately after admission, 30 ml of sedimentated blood cells was given through the umbilical arterial catheter by a slow push. Neonatal beat-to-beat heart rate monitoring, which was started within the first few minutes of life, showed a baseline heart rate of 160 to 170 bpm with lack of short-term variability but with periods of a sinusoidal pattern, both prior to and after the initial transfusion. A capillary blood sample obtained at 12 minutes showed a Pco2 of 44 torr, a Pao<sub>2</sub> of 40 torr, a base deficit of 9 mEq, and a hematocrit of 17%. The sinusoidal heart rate pattern, which was noted since birth, persisted for the first 3 hours of life until, during a one-volume exchange transfusion, the pattern disappeared. The baseline heart rate remained at 140 to 145 bpm, but beat-to-beat variability was significantly decreased. During the same period arterial pH values were 7.35, 7.36, and 7.43, with a Pao<sub>2</sub> of 43, 53, and 61 torr during administration of 35% to 37% oxygen. Over the next few hours the baseline heart rate decreased to 130 bpm with increasing beat-to-beat variability. Fig. 3 shows serial recordings of the neonatal heart rate during the first 2 hours, after the first one-volume exchange transfusion, and on the fourth day of life.

The mean arterial blood pressure ranged from 41 to 48 torr for the first 24 hours of life. Subsequent to the initial one-volume exchange, the infant had four double blood volume exchange transfusions and phototherapy. Significant problems during the first few days were transient throm-bocytopenia and hypocalcemia, which resolved with therapy. The infant was discharged home on the tenth day of life with a weight of 2,720 gm and in apparent good condition.

As experience with FHR monitoring grows, understanding of the pathophysiology of the fetal cardiovascular response to stressful situations also increases. The physiologic events which trigger a sinusoidal heart rate in the fetus occur in a number of different fetal environments and attempts to explain the reason for the pattern fail to encompass all reported clinical states. Rochard and associates1 attribute the pattern to an absence of autonomic nervous system control over the heart. This theory would fail to explain the occurrence of the pattern following intrauterine fetal transfusion. Modanlou and associates<sup>2</sup> hypothesized a high-output fetal cardiac failure as the mechanism of the sinusoidal FHR pattern, but that fails to explain the terminal patterns seen in some asphyxiated fetuses. A recent report in the literature described the temporary occurrence of a sinusoidal pattern following intramuscular administration of alphaprodine for pain relief in labor. The significance of this occurrence is unknown and confirmatory studies need to be performed.

Although the initial trigger for the loss of normal

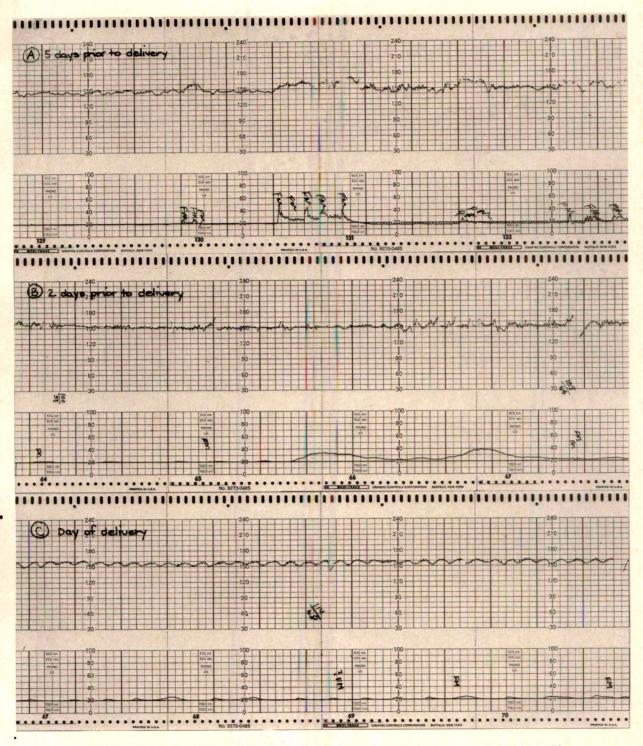


Fig. 2. Nonstressed recordings of FHR. Panel A, 5 days prior to delivery, shows accelerations with fetal movement. Panel B, 2 days prior to delivery, shows a decrease in the reactivity and variability. Panel C, on the day of delivery, the sinusoidal pattern of the FHR is noted.

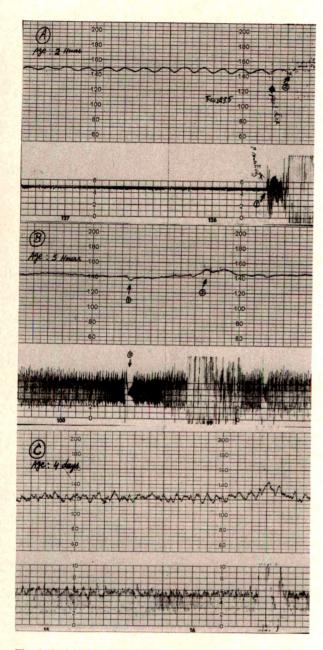


Fig. 3. Serial recordings of the neonatal beat-to-beat variability (upper panels) and the respiratory breath-to-breath pattern by impedance pneumotachograph (lower panels). A: Recordings at 2 hours of age showing sinusoidal FHR pattern. At point (1) the sensitivity of the pneumotachograph was increased and at point (2) heel-stick blood sampling was performed. B: Recordings at 5 hours of age. Sinusoidal FHR pattern has disappeared, but baseline variability remains minimal. At point (1) infant had a short period of apnea associated with slight bradycardia. At point (2) there is a higher amplitude of the respiratory pattern associated with crying and corresponding tachycardia. C: Recordings at 4 days of age. Note regular breathing pattern and significantly increased neonatal heart rate variability with baseline about 120 bpm. Increased neonatal heart rate with crying is also noted in this recording.

sympathetic and parasympathetic control of the fetal heart rate may vary, a possible common pathway is tissue hypoxia of the fetal heart and central nervous system. The sinusoidal pattern in our case also was evident in the newborn infant, despite normal arterial Po<sub>2</sub> values. The fact that the pattern disappeared during exchange transfusion may point toward tissue hypoxia as the etiology. Why this FHR pattern is seen only in some cases of Rh isoimmunization, severe anemia, asphyxia, etc., is unclear, but the occurrence of a sinusoidal pattern remains an ominous circumstance.

While the sinusoidal FHR pattern may represent local tissue hypoxia, it is not pathognomonic of any specific fetal condition but must be regarded as ominous.

This case also demonstrates that a steadily declining pattern of  $\Delta OD_{450}$  values can be misleading and that adjunctive FHR monitoring can complement ultrasound and amniocentesis in the management of the Rh-isoimmunized pregnancy.

#### REFERENCES

- Rochard, F., Schifrin, B., Goupil, F., et al.: Nonstressed fetal heart rate monitoring in the antepartum period, Am. J. Obstet. Gynecol. 126:699, 1976.
- Modanlou, H., Freeman, R., Ortiz, O., et al.: Sinusoidal fetal heart rate pattern and severe fetal anemia, Obstet. Gynecol. 49:537, 1977.

# Pseudocyesis and sonography

GAY M. GUZINSKI, M.D.
SUZANNE H. CONRAD, M.D.

Departments of Obstetrics and Gynecology and Radiology, University of Washington, Seattle, Washington

Throughout recorded history there are sporadic reports of patients presenting with symptoms and signs of pregnancy who, in fact, are not carrying a fetus. This false pregnancy may be due to a combination of depression and an intense desire and/or fear about pregnancy. Some cases of pseudocyesis are detected during the course of prenatal care while others come to the attention of a health care provider only when they have an unproductive episode of "labor." The endocrine and psychological derangements, which are both concomitant and causal, are not yet fully described. A recent paper in the literature reviews and summarizes what is currently known in this regard.

Making the diagnosis of pseudocyesis can be surprisingly difficult, since there are even some reported cases

Reprint requests: Dr. Gay M. Guzinski, Department of Obstetrics and Gynecology, University Hospital, 1959 N. E. Pacific St., Seattle, Washington 98105.

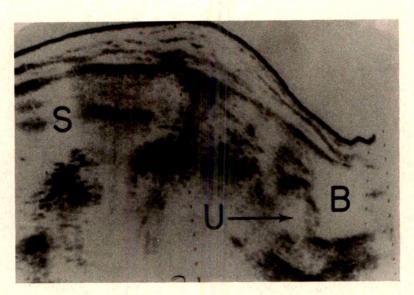


Fig. 1. Case No. 1: Longitudinal scan 2 cm to the left of the midline: B = Bladder; U = nonpregnant uterus; S = stomach. Dotted line indicates level of the umbilicus and the inferior margin of the stomach.

in which the pregnancy test was positive. Patients with this problem usually report signs and symptoms of pregnancy such as amenorrhea, nausea, breast tenderness, and abdominal distention. Indeed their conviction of pregnancy is so strong that the physician may not consider false pregnancy even after having difficulty detecting fetal heart tones or fetal movement.<sup>2</sup> Some patients have normal prenatal care, and the lack of a fetus only comes to light when "labor" fails to produce one.

The presence of a normal-sized uterus and the absence of a fetus are, of course, the ultimate confirmatory evidence that the patient is not physiologically pregnant. The abdominopelvic examination may not be helpful because of such factors as obesity or lack of patient cooperation, in which case an examination with the use of anesthesia, abdominopelvic radiography, or ultrasound study can be performed.

During general anesthesia the abdominal musculature relaxes and a normal-sized uterus can usually be palpated, but this procedure is costly and constitutes some hazard to the patient's life. A pelvic x-ray film can be used to detect fetal parts, but since it cannot detect fetal movement or cardiac activity, some question may arise about fetal death. Sonography provides clear evidence of both fetal movement and heart activity as well as documenting fetal size and position or lack thereof.

Reports of three cases in which confirmation and/or establishment of the diagnosis of pseudocyesis was made by ultrasound are given below.

In Case 1, a 19-year-old black woman reporting an 8-month pregnancy presented for evaluation of lower abdominal pain. In the original emergency room evaluation the abdomen wasnoted to be distended, and no fetal heart tones were heard,

but fetal movements were felt by the examiner and the fetus was described as "head down, back L.: The patient was admitted to the obstetric service and an ultrasound examination was performed. This revealed a small, nonpregnant uterus and a large, left upper quadrant mass, thought to be the stomach (Fig. 1). This was proved when placement of a nasogastric tube resulted in relief of gastric dilatation, and the abdomen returned to normal size.

In Case 2, a 24-year-old Indian woman, gravida 5, para 2, abortions 3 (?), was admitted from the jail in possible premature labor. She reported a positive pregnancy test approximately 8 months prior to evaluation but had not had prenatal care. There had been decreased fetal movement, according to her, along with back pain and vaginal spotting the night before admission. No gravid uterus was palpable, but she was too obese to permit definitive examination, and sonography was ordered. The examination revealed a nonpregnant uterus with a small cystic structure in the left adnexal area, and the patient was discharged from the obsetrics service.

In Case 3 a 25-year-old white woman was admitted to the medical service and was noted to have an enlarged abdomen with what was though to be a right lower quadrant mass. She was a known schizophrenic, however, and a history was not easily obtainable. The obstetrics and gynecology consultant who examined her reported hearing fetal heart tones with both the fetoscope and the Doppler instrument and noted a 24 cm midline abdominal mass, thought to be a gravid uterus. An ultrasound examination was done to determine gestational age, at which time a nonpregnant uterus and a large cystic mass were noted. Following catheterization of the urinary bladder with removal of 1,000 ml of urine the mass and the abdominal distention disappeared. The patient was discharged to a treatment facility capable of handling her psychiatric problem.

Ultrasound examination of patients suspected of having pseudocyesis can provide relatively low-cost,

safe, definite diagnostic evidence of the nonpregnant state. It can also fortuitously diagnose the condition when it is not suspected and give clues to other abnormalities such as bladder distention. This information then allows the clinician to institute appropriate diagnostic and therapeutic measures and gives the patient visible evidence that no fetus is present.

#### REFERENCES

- Murray, J. L., and Abraham, G. E.: Pseudocyesis: A review, Obstet. Gynecol. 51:627, 1978.
- Bivin, G. D., and Klinger, M. P.: Pseudocyesis, Bloomington, 1937, Principia Press.

# Lecithin/sphingomyelin ratio in amniotic fluid obtained vaginally

ARNOLD S. GOLDSTEIN, M.D. HENRY H. MANGURTEN, M.D. JOSEPH V. LIBRETTI, M.D. ARNOLD M. BERMAN, M.D.

Departments of Pediatrics and Obstetrics and Gynecology, Lutheran General Hospital, Park Ridge, Illinois

THE LECITHIN/SPHINGOMYELIN (L/S) ratio in amniotic fluid is a reliable indicator of fetal pulmonary maturity.¹ Fluid for this determination is usually obtained by transabdominal amniocentesis, but after rupture of the membranes (ROM) it may not be possible to collect a sufficient sample. A L/S ratio of amniotic fluid obtained vaginally would be useful, but there is doubt concerning the ability to measure the ratio and its reliability when amniotic fluid is mixed with vaginal contents.²

This study shows that a valid L/S ratio can be determined from amniotic fluid obtained vaginally. Furthermore, it supports the theory that prolonged ROM may result in a decreased incidence or severity of the respiratory distress syndrome (RDS).<sup>3</sup>

The patients in this study were women admitted to the labor area of Lutheran General Hospital with ruptured membranes. Fifty patients were included, without selection, over a 1-year period. Fluid was collected in a clean bedpan by gravity and immediately frozen for later determination of the L/S ratio. Currently accepted obstetric practice was followed without knowledge of the experimental L/S ratio results. The thin-layer chromatography method of Borer and associates<sup>4</sup> was used to measure the L/S ratios.

The study includes 51 attempts to collect fluid from

Reprint requests: Henry H. Mangurten, M.D., Director, High-Risk Nursery, Lutheran General Hospital, 1775 West Dempster, Park Ridge, Illinois 60068.

**Table I.** Preterm infants with mature L/S ratios ( $\geq 2.0$ )

Length of gestation (weeks)	Time from rupture of membranes to collection of amniotic fluid	Time from collection to delivery	Total time of ruptured membranes
37	33 hr	9 hr	42 hr
37	9 days	4 hr	9+ days
37	l hr	4 hr	5 hr
37	6½ hr	3½ hr	10 hr
37	2 hr	15 hr	17 hr
37	22 hr	14 hr	36 hr
36	1½ hr	2½ hr	4 hr
34	39 hr	11½ hr	50½ hr
34	9½ hr	18½ hr	28 hr
32	78½ hr	11 hr	89½ hr
31	2 wk	0	2 wk

None developed RDS.

50 patients. Three attempts were unsuccessful. Six collections were discarded: One specimen resulted in a poor separation of spots on chromatograph; three specimens were mixed with urine which precluded interpretation; and two specimens were considered invalid because they had more than 3% red blood cells by volume. The 42 remaining specimens resulted in routine interpretations. (Of these, three were partially contaminated by blood and/or urine but in quantities that did not interfere with the analyses.)

The L/S ratio was mature ( $\geq 2.0$ ) in 37 of the specimens, and none of these infants developed RDS. Included in this group was an infant born at 31 weeks' gestation to a mother whose membranes had ruptured 2 weeks prior to amniotic fluid collection; this infant subsequently developed fatal necrotizing enterocolitis. One infant born at 32 weeks' gestation to a diabetic mother whose membranes had been ruptured almost 4 days developed transient tachypnea of the newborn but recovered without complication. A term infant . born after rupture of the membranes several minutes earlier had asphyxia neonatorum but was easily resuscitated and did well thereafter. Another term infant was meconium stained but did not develop any problems. The other 33 infants with mature L/S ratios had no symptoms and included six 37-week gestations, one 36week gestation, and two 34-week gestations. The durations of rupture of the membranes of all the preterm infants with mature L/S ratios are shown in Table I.

Two infants had transitional L/S ratios (1.5 to 1.9). They were born at term and had uneventful courses. Three infants had immature (<1.5) values. Their gestations were less than 32 weeks. One died in utero; one developed severe RDS and died; and one developed moderate RDS and survived. L/S ratios in all three were obtained at or less than 1 hour after rupture of the membranes. Table II shows gestational ages, dura-

Table II. Gestational ages, durations of rupture of membranes, and outcomes in five infants with transitional and immature L/S ratios

L/S ratio	Length of gestation (weeks)	Time from rupture of membranes to collection of amniotic fluid	Time from collection to delivery	Total time of ruptured membranes	Outcome (RDS)
T (1.5-1.9)	40	4½ hr	11 hr	15½ hr	No RDS
T (1.5 1.5)	38	0	6 hr	6 hr	No RDS
I (<1.5)	31+	0	15 min	15 min	Moderate
I	20-22	1 hr	0	1 hr	Stillborn
I	29	0	11 hr	11 hr	Severe—fata

T = Transitional; I = immature.

tions of rupture of the membranes, and outcomes of these five infants.

When amniotic membranes are ruptured and transabdominal amniocentesis might not provide a sufficient sample, amniotic fluid obtained vaginally can be tested if determination of an L/S ratio is indicated. In this study, sufficient fluid was obtained 48 times in 51 attempts (94%). Six of the 48 samples either were discarded because of contamination or resulted in poor spot separation. An L/S ratio was thus reported for 87.5% of the specimens.

There is uncertainty regarding the reliability of correlating the L/S ratio from amniotic fluid collected vaginally with fetal maturity and subsequent morbidity. There were not enough immature ratios in this study to provide meaningful statistical analysis. The raw data suggest, however, that these values are useful. Eleven preterm and 26 term infants had mature ratios and did not develop RDS. Three preterm infants had immature ratios: One infant was stillborn; the other two infants developed RDS, and one of these died. The two infants with transitional L/S ratios were born at term and did not develop RDS.

Seven infants had gestations of less than 36 weeks. Three of these infants had immature L/S ratios with intervals between rupture of the membranes and specimen collection of 0, 1, and 0 hours; as previously noted, two of these infants subsequently developed RDS. The other four infants had mature L/S ratios with durations of rupture of the membranes before specimen collection of 9½ hours, 39 hours, 3¼ days, and 2 weeks; none of these infants developed RDS. These data support the theory that prolonged (more than 16 or 24 hours) rupture of the membranes³ enhances pulmonary maturity with resultant decreased incidence of RDS.

#### REFERENCES

- Gluck, L., Kulovich, M. V., Borer, R. C., Jr., Brenner, P.H., Anderson, G. G., and Spellacy, W. N.: Diagnosis of the respiratory distress syndrome by amniocentesis, Am. J. Obstet. Gynecol. 109:440, 1971.
- 2. Gluck, L.: Personal communication.

- Bauer, C. R., Stern, L., and Colle, E.: Prolonged rupture of membranes associated with a decreased incidence of respiratory distress syndrome, Pediatrics 53:7, 1974.
- Borer, R. C., Jr., Gluck, L., Freeman, R. K., and Kulovich, M. V.: Prenatal prediction of the respiratory distress syndrome, Pediatr. Res. 5:655, 1971.

# Accidental puncture of pelvic kidney: A rare complication of culdocentesis

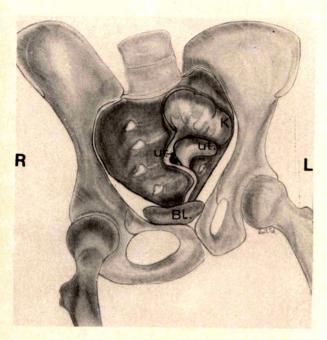
MENACHEM GRANAT, M.D. THOMAS GORDON, M.D. ELIAS ISSAQ, M.D. MOSHE SHABTAI, M.D.

Department of Urology and Department of Obstetrics and Gynaecology, Rothschild University Hospital, Faculty of Medicine, Technion, Haifa, Israel

ACCIDENTAL DAMAGE to a pelvic kidney in the course of culdocentesis, leading to massive blood loss, is presented. No such cases involving culdocentesis have been reported previously. The importance of bearing in mind the possible existence of a pelvic kidney, when culdocentesis is attempted, is stressed.

A 21-year-old woman, gravida 1, para 1, presented in the emergency ward after midnight with lower abdominal pain, associated with vomiting and bloody vaginal discharge, which was unlike her normal menses. Her last menstrual period was 5 weeks earlier. She reported, that 2 months previously an intrauterine contraceptive device had been inserted but was removed because of excessive bleeding. Otherwise, past history was unremarkable. She reported having a regular menstrual cycle of 25 to 28 days. On admission the patient was in good general condition. Temperature was normal. Pelvic examination disclosed a somewhat thickened and tender left parametrium and a fixed cystic mass, 5 cm in diameter, to the left of the uterus, which was thought to be an ovarian cyst.

Reprint requests: Dr. M. Granat, Department of Obstetrics and Gynaecology, Hadassah University Hospital, Ein Karem, Jerusalem, Israel.



**Fig. 1.** Schematic illustration of the anatomic relations at the operation (right oblique view). K. = Kidney; ut. = uterus; ut. = ureter; BL. = urinary bladder.

Laboratory examination revealed a hemoglobin of 13.8 gm/100 ml, and a white blood cell count of 7,000/cu mm. Urinalysis was normal. Subsequently urine culture was found to be sterile and the level of the beta subunit of human chorionic gonadotropin in the serum was reported as negative.

Attempting to test the possibility of a ruptured ectopic pregnancy, the junior resident on duty performed culdocentesis (with a size 18 needle), and 10 ml of fresh blood was drawn. Curettage yielded only scanty material, which was subsequently defined as slightly secretory endometrium. A laparoscopy was immediately performed and revealed normal genitalia with no blood in the cul-de-sac and no signs of tubal pregnancy. Posterior and to the left of the uterus, a soft extraperitoneal mass, estimated at 10 cm in diameter, was observed. With the suspicion of a pelvic kidney, intravenous pyelography was performed and demonstrated a left ectopic kidney with apparently normal excretion and typical anterior malrotation. The right kidney was at its normal position and slightly malrotated.

Because of the improvement in the patient's general condition, she was discharged from the hospital on the third day with a referral to the Gynaecological and Urological Outpatient Clinics.

Five days later, the patient was readmitted to the Urological Service with the complaint of lower abdominal pain and a temperature of 38.3° C. On examination, marked tenderness was noted in the lower abdomen and a poorly defined mass was palpated in the left lower quadrant. Antibiotic treatment was initiated with 4 gm of ampicillin and 2 gm of sodium cloxacillin per day, under the working assumption that the patient's condition was consistent with pelvic inflammatory disease, either caused or exacerbated by the diagnostic manipulations on her previous admission.

The following day, examination revealed enlargement of the abdominal mass, which was exquisitively tender, and a

rightward displacement of the uterus. Additional intravenous pyelography revealed an apparently nonfunctioning pelvic kidney with dilatation of the right renal pelvis and ureter. Measurement of hemoglobin at that point was 8.5 gm/100 ml. Retroperitoneal bleeding was suspected and an explorative laparotomy was immediately performed. A retroperitoneal mass was found, consisting of a large subcapsular hematoma surrounding a pelvic kidney. A small puncture wound was detected in the lower pole, through which blood was steadily oozing. The laceration was sutured and the bleeding stopped. The renal pelvis and ureter were explored and found to be intact. The close proximity of the ectopic kidney to the internal genitalia, as was found during the operation, is illustrated in Fig. 1. The postoperative course was uneventful, and control intravenous pyelography, performed 20 days after the operation, again demonstrated normal filling of the left ureter. Concomitant hysterosalpingography revealed an elongated and fixed left tube with sactosalpinx.

Culdocentesis, being a "blind procedure," is potentially dangerous, especially in the presence of adhesions obliterating the cul-de-sac. Nevertheless, it is still widely used in gynaecologic practice, serving as either an emergency procedure for the diagnosis of ectopic pregnancy<sup>1</sup> or as an early diagnostic aid for detection of ovarian carcinoma.<sup>2</sup>

In general, no serious accidents have been ascribed to this procedure. Funkhouser and associates² reported the incidence of bowel penetration to be 1.4% but emphasized the lack of subsequent complications. Lucas and Hassim¹ also stated that with a size 18 needle even a perforation of a pyosalpinx or adjacent bowel did not lead to complications.

The high diagnostic yield of culdocentesis in cases of ectopic pregnancy, coupled with its simplicity, have given the procedure a central role in the rapid diagnosis of this common gynecologic emergency.<sup>3, 4</sup> Paradoxically its routine use in the hands of an inexperienced junior resident on call late at night may pose potential hazards to the patient. Such was the situation in the case at hand, when puncture of an ectopic pelvic kidney with subsequent complications was the result.

Pelvic kidney occurs approximately once in 800 persons and is often associated with genital malformation. It may cause obstetric difficulties or lead to unnecessary operation as a result of the misdiagnosis of pelvic tumor. No reports have yet appeared in the literature regarding the accidental involvement of a pelvic kidney in culdocentesis. In the case reported here the patient presented with abdominal pain of unknown origin, which retrospectively might have been related to poor drainage due to malrotation of the ectopic kidney, as frequently occurs in this situation. Another possible source of our patient's abdominal pain might be the exacerbation of latent chronic pelvic inflammatory disease, which was only demonstrated 20 days after the operation by hysterosalpingography.

The finding of a pelvic kidney, albeit rare, must be taken into account by the gynecologist during potentially hazardous procedures. Whenever its presence is

known or suspected, it is advisable to avoid culdocentesis, and alternative procedures, such as laparoscopy for the diagnosis of ectopic pregnancy, should be undertaken. The availability of sensitive assays for the beta subunit of human chorionic gonadotropin undoubtedly lessens the need for surgical intervention when the diagnosis of tubal pregnancy has to be excluded.

# REFERENCES

- Lucas, C., and Hassim, A. M.: Place of culdocentesis in the diagnosis of ectopic pregnancy, Br. Med. J. 1:200, 1970.
- Funkhouser, J. W., Hunter, K. K., and Thompson, N. J.: Diagnostic value of cul-de-sac aspiration in detection of ovarian carcinoma, Acta Cytol. (Baltimore) 19:538, 1975.
- 3. Armstrong, J. T., Wills, S. M., Moore, J., and Lauden, A. E.: Ectopic pregnancy. A review of 481 cases, Am. J. Obstet. Gynecol. 77:364, 1959.
- Hlavin, G. E., Ladocsi, L. T., and Breen, J. L.: Ectopic pregnancy: An analysis of 153 patients, Int. J. Gynaecol. Obstet 16:42 1978

# Real-time ultrasonography in the evaluation of urinary stress incontinence

ROLFE D. WHITE, M.D., LIEUTENANT, MC, USNR

DENNIS McQUOWN, M.D.

THOMAS A. McCARTHY, M.D.

DONALD R. OSTERGARD, M.D., F.A.C.O.G.

Women's Hospital, Memorial Hospital Medical Center of Long Beach, Long Beach, California; the Department of Obstetrics and Gynecology, Los Angeles County, Harbor/University of California (Los Angeles) Medical Center, Torrance, California; the Department of Obstetrics and Gynecology, Naval Regional Medical Center, Portsmouth, Virginia

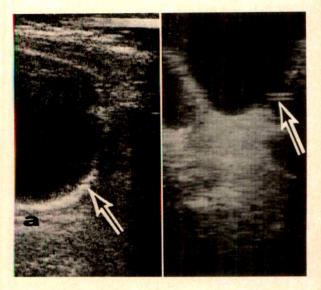
MOST AUTHORITIES on stress urinary incontinence indicate that the primary etiologic factor is the loss of support of the bladder base, vesical neck, and proximal urethra. Since there may be other primary or concomitant causes of incontinence that are not easily ascertained through history and physical examination alone, an accurate diagnosis necessitates other laboratory tests and procedures.

Standard evaluation procedures include various ra-

This study was sponsored and supported by the Bureau of Medicine and Surgery, Clinical Investigation Program.

The opinions or assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of their respective institutions, the Department of the Navy, or the Department of Defense.

Reprint requests: Lieutenant Rolfe D. White, MC, USNR, Department of Obstetrics and Gynecology, U.S. Naval Regional Center, Okinawa, Japan, FPO Seattle, Washington 98778.



**Fig. 1.** The normal female urethra. *a,* Without catheter. *b,* With plastic Fr. 6 pediatric feeding tube within the urethra. The arrows indicate the location of the urethra.

diographic techniques, such as cystourethrography, with and without fluoroscopy, and beaded chains to demonstrate the anatomy of the lower urinary tract. Few of these procedures accurately define dynamic function of the urethrovesical unit.

Holmes<sup>2</sup> was the first to demonstrate the ease and accuracy of evaluating the static urinary bladder with ultrasonic techniques in terms of residual urine, the mobility of the bladder wall, distortion of the bladder contour by adjacent pelvic pathologic conditions, and detection and evaluation of bladder tumors.

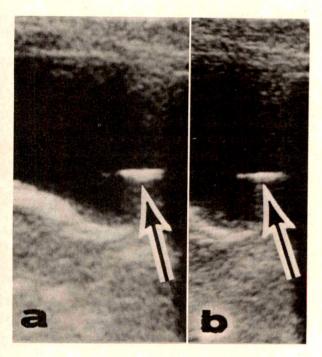
This is the first report in the English language of a new, simplified technique that utilizes the portable linear-array, real-time ultrasound machine to provide accurate information regarding the anatomic relationships of the urethra to the bladder.

Ultrasound examinations of the bladder and urethra were performed in 30 women after a thorough genitourinary history was obtained. Ages of the women ranged from 16 to 62 years and parity was from 0 to 6. Ten had urethral catheters in place during the procedure and most underwent ultrasound for unrelated indications. Both continent and incontinent patients participated in these evaluations.

The ultrasound equipment used for these studies included two portable linear-array, real-time scanning machines: Advanced Diagnostic Research (ADR) Model 2130\* and Toshiba Model SAL-204.† The Toshiba transducer was 2.4 MHZ and the ADR transducer was 3.5 MHZ. The illustrations presented are those taken

\*Advanced Diagnostic Research, 2224 S. Priest Dr., Tempe, Arizona 85282.

†Toshiba Medical Systems, 1145 Dominguez, Carson, California 90745.



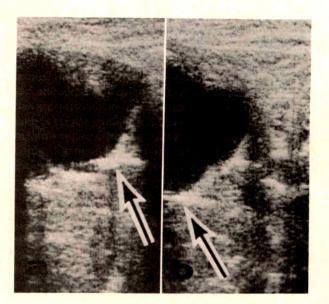
**Fig. 2.** The normal female urethra with catheter in place. *a*, Resting. *b*, Straining. The arrows indicate the urethra and the clearly evident echos from the walls of the catheter. There is minimal descent of the urethrovesical junction with straining.

from the Toshiba machine with its accompanying Polaroid camera system.

The patient arrived for the examination with a full bladder or drank water while awaiting for examination. After placement of a Fr. 6 or 8 soft plastic pediatric feeding tube through the urethra into the bladder by means of a sterile technique, the physician scanned the bladder and urethra in both the supine and standing positions. Scanning also included longitudinal, transverse, and oblique techniques while the transducer was angled caudally from above the pubic symphysis to visualize clearly the urethra and bladder wall. The patient coughed and performed a Valsalva's maneuver in each scanning plane.

With the patient in both the supine and standing positions the physician measured the angle of urethral inclination and the distance between the pubic symphysis and the urethrovesical junction with and without the Valsalva's maneuver.

In this series, real-time ultrasonography demonstrated the urethra and the urethrovesical junction without instrumentation in seven of 20 patients and in all catheterized patients (Fig. 1). Fig. 2 demonstrates typical findings in a continent patient who had little change in the relative anatomic position of the urethrovesical junction with the Valsalva's maneuver. Similarly, real-time ultrasound clearly demonstrated the altered urethrovesical relationships in incontinent patients with straining (Fig. 3).



**Fig. 3.** The female urethra in the incontinent patient. *a*, **Resting.** *b*, Straining. The arrows indicate the urethra. There is marked descent of the urethrovesical junction with straining.

Minimal difficulties were encountered in five patients, two of whom were extremely obese and three of whom had pubic symphysis "shadowing" that obscured visualization of the urethra.

Real-time ultrasound effectively demonstrates the anatomic relationship of the urethra and the bladder in both normal and incontinent patients during static and dynamic functional states. Although ultrasound demonstrated the urethras in half of the noncatheterized patients, the placement of a Fr. 6 to 8 pediatric feeding tube allowed visualization of the urethrovesical junctions in all patients.

Many authors stress the importance of cystoure-thrography as a valuable diagnostic tool to provide information regarding the posterior urethrovesical angle, the angle of inclination of the urethral axis, the flatness of the bladder base, and the location, the mobility, and the funneling of the urethrovesical junction both at rest and with the stress of a Valsalva's maneuver. 1. 3–5 This report describes a technique which avoids exposure of the patient to x-irradiation and provides information similar to that obtained with radiographic studies.

The potential advantages of this technique are many. It can be performed in the office with a machine that will probably be in common usage by most obstetrician-gynecologists in the next decade. It requires very little expertise, is a rapid test, is safe and involves minimal discomfort, avoids x-irradiation, and is easily repeated.

Although ultrasound provides a great deal of information regarding urethrovesical relationships, it is not

a means of diagnosing urinary stress incontinence. When complemented by a detailed history and clinical examinations, as well as other procedures, such as cystometry, cystourethroscopy, urethral closure pressure profiles, studies of urethrovesical pressure dynamics, and uroflowmetry, it significantly aids the clinician in the evaluation of women with lower urinary tract symptomatology.

We appreciate the assistance and encouragement of Nancy Worthen, M.D., Division of Diagnostic Ultrasound, Los Angeles County Harbor/University of California (Los Angeles) Medical Center, Torrance, California, and Elizabeth Williams, R.D.M.S., Memorial Hospital Medical Center of Long Beach, Long Beach, California.

#### REFERENCES

 Graber, E. A.: Stress incontinence in women: a review— 1977, Obstet. Gynecol. Surv. 32:565, 1977.

2. Holmes, J. H.: Ultrasonic studies of bladder filling and contour, in Hinman, F. J., editor: Hydrodynamics of Micturition, Springfield, Illinois, 1971, Charles C Thomas, Publisher, p. 303.

 Schonberg, L. A.: Urethrocystography, a practical office procedure in the evaluation and treatment of stress incontinence, Am. J. Obstet. Gynecol. 86:995, 1963.

 Stanton, S. L.: Radiology, in Stanton, S. L., editor: Female Urinary Incontinence, London, 1977, Lloyd-Luke, Publisher, p. 39.

 Tanagho, E. A.: Simplified cystography in stress urinary incontinence, Br. J. Urol. 46:295, 1974.

# Oral contraceptive-induced chorea

NAOMI KAPLINSKY, M.D. MICHAEL THALER, M.D. OTTO FRANKL, M.D.

Department of Medicine, Chaim Sheba Medical Center, Tel-Hashomer, Israel

A PATIENT with oral contraceptive-induced chorea is described. The chorea was not suppressed by propranolol but disappeared gradually within 10 weeks. This is a relatively rare complication of, but the importance of its recognition is obvious.

Reprint requests: Dr. Naomi Kaplinsky, Department of Medicine, Chaim Sheba Medical Center, Tel-Hashomer, Israel.

An 18-year-old woman presented to the Chaim Sheba Medical Center with the complaint of involuntary movements of both upper extremities and the face initially noted 4 months prior to admission. She was given an oral contraceptive 2 months before the appearance of those movements. There was no history of rheumatic fever, heart disease, previous chorea, central nervous system involvement, weakness, or other neurological symptoms. She was not receiving other medications and family history was negative for chorea and any other movement disorder. Past history was nonrevealing except for a tendency to develop skin abscesses since childhood.

On physical examination no abnormality was found except for choreoathetoid movements of the upper extremities, more on the right, and grimaces exacerbated by stress. Electrocardiogram and electroencephalogram were normal, as were routine laboratory examinations including erythrocyte sedimentation rate, complete blood count, glucose, urea, antistreptolysin titer, and protein electrophoresis. There was no antinuclear factor and culture from the pharynx was sterile.

The oral contraceptive was discontinued. An attempt to suppress the choreiform movement with propranolol up to 30 mg four times a day was unsuccessful. Reduction of the choreiform movement was noted 1 month after the oral contraceptive was discontinued; the grimaces disappeared, and her handwriting was readable again. Complete resolution was observed within 10 weeks.

Choreiform movement is one of the rare side effects of oral contraceptives<sup>1, 2</sup>; it is more common in patients with a previous history of rheumatic fever, Sydenham's chorea, or chorea gravidarum. This side effect disappears following discontinuation of the drug. Chorea can be a manifestation of rheumatic fever, systemic lupus erythematosus, or drug intoxication. These were excluded in the patient described. Propranolol was tried because of its known effect in familial and senile tremor. The etiology of oral contraceptive–induced chorea is not known. It might be vascular, immunologic, or neurotransmitted abnormalities.

Clinicians must be aware of this potential side effect of oral contraceptives since the chorea can be "cured" easily by stopping the drug.

### REFERENCES

- Gamboa, E. T., Isaacs, G., and Harter, D. H.: Chorea associated with oral contraceptive therapy, Arch. Neurol. 25:112, 1971.
- Pulsinelli, W. A., and Hamill, R. W.: Chorea complicating oral contraceptive therapy, Am. J. Med. 65:557, 1978.

# BOOKS

# Books received

- Catalog of Teratogenic Agents. Third Edition. Thomas H. Shepard. 410 pages. Baltimore, 1980, The Johns Hopkins University Press. \$25.00.
- Control of Human Reproduction. R. L. Holmes and C. A. Fox. 149 pages, illustrated. New York, 1979, Academic Press, Inc. \$12.50 (soft cover).
- Female sterilization by Minilaparotomy or Open Laparoscopy. A. Joseph Penfield. 136 pages, illustrated. Baltimore, 1980, Urban & Schwarzenberg. \$16.50.
- Human Reproduction Conception and Contraception. Second Edition. Edited by E. S. E. Hafez. 934 pages, illustrated. Philadelphia, 1980, Harper & Row, Publishers, Inc. \$47.50.
- The Infertile Female. Edited by James R. Givens. 545 pages, illustrated. Chicago, 1979, Year Book Medical Publishers, Inc. \$45.95.

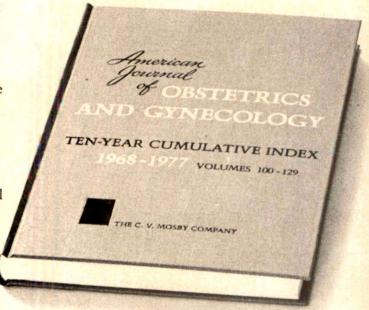
- Practical Clinical Cytology. Virginia A. Livolsi. 335 pages, illustrated. Springfield, Illinois, 1980, Charles C Thomas, Publisher. \$32.50.
- Steroid Hormones. D. B. Gower. 115 pages, illustrated. Chicago, 1979, Year Book Medical Publishers, Inc. \$6.95 (soft cover).
- Vaginal Contraception: New Developments. PARFR Series on Fertility Regulation. Edited by Gerald I. Zatuchni, Aquiles J. Sobrero, J. Joseph Speidel, and John J. Sciarra. 389 pages, illustrated. Philadelphia, 1979, Harper & Row, Publishers. \$17.50.

# New! Available for the first time

The ten-year cumulative author and subject index to volumes 100-129 (1968-1977) of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY is now available for your journal collection. It is a complete and comprehensive reference guide to over 28,000 pages of authoritative articles published in the Journal during the past ten years.

The world-renowned "Gray Journal" is the oldest specialty journal devoted to obstetrics and gynecology.

Now these influential papers, appearing between 1968-1977, have been cross-referenced to include over 23,100 subject entries. Each entry lists the complete article title, author(s), volume, page, and year of publication.



The author index lists more than 13,850 contributors from this period, along with respective article title, author-to-author referral, volume, page, and publication date.

The 479-page index is handsomely presented in a rust and gold cloth-cover volume. It is a must for every library concerned with obstetrics and gynecology. Send for your copy of this valuable reference today!

479 pages, 81/4" × 11", Price: \$31.75 U.S.A.; \$40.25 Canada; \$33.50 all other countries.

#### YES!

Complete and mail today to The C. V. Mosby Company, Attn: Order Processing Dept., 11830 Westline Industrial Drive, St. Louis, Mo. 63141

### OBSTETRICS— GYNECOLOGY

Unique opportunity exists for Board Certified/Eligible Obstetrician-Gynecologist seeking a full time position in a multi-specialty group practice.

In addition to an active practice the position offers opportunity for teaching in a residency training program, clinical research, and participation in an active adolescent maternity program.

Excellent incentive compensation system with guaranteed base salary and fringe benefits. Begin summer 1981 or sooner.

Send vitae in confidence to:

William F. Grace, M.D., F.A.C.O.G.
Director, Ob/Gyn Division
GENESEE HEALTH SERVICE
MEDICAL GROUP

220 Alexander Street Suite 708 Rochester, New York 14607 (716) 263-5214

An Equal Opportunity Employer, M/F.

### FACULTY POSITIONS OBSTETRICS AND GYNECOLOGY UNIVERSITY OF TENNESSEE

#### Clinical Education Center Chattanooga

Positions available in Perinatology and Ambulatory Care in the Department of Obstetrics and Gynecology at the Clinical Education Center at Chattanooga. Obstetrics and Gynecology Residency Program in a University Affiliated Hospital. Approved program with ten residents. Rotation of Medical Students for Core Clerkships and Electives. Faculty appointment. Must be Board Certified Obstetrics and Gynecology. Please direct inquiries and C. V. to:

Norman L. Stahl, M.D. Chairman, Department of Obstetrics and Gynecology Suite 400-921 East Third Street Chattanooga, Tennessee 37403 Phone (615) 756-4856

The University of Tennessee is an Affirmative Action and Equal Employment Opportunity Employer

#### MATERNAL — FETAL MEDICINE

The Department of Obstetrics and Gynecology of the Baystate Medical Center in Springfield, Massachusetts, is seeking a full time Director for its Perinatal program. There are 5,000 in-house deliveries as well as 5,000 deliveries in 7 affiliated hospitals for this Perinatal system. The Department is affiliated with both Tufts and the University of Massachusetts Schools of Medicine. The Department has 40 community based Obstetricians-Gynecologists, 16 residents, and 4 additional full time faculty. The candidate must be board eligible in Maternal-Fetal Medicine. Salary and academic rank are commensurate with training and experience. Those interested please send CV to: Laurence E. Lundy, M.D., Chairman, Department of OB-GYN, Baystate Medical Center, 759 Chestnut Street, Springfield, Massachusetts 01107.

An Equal Opportunity Employer M/F/H

#### PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in these specially designed library file cases. Designed to keep your journal copies near at hand in your office, library, or home.

Your case is heavy bookbinder's board in rich red Kivar cover. Files are scuff-resistant and washable.

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding.

Files are reasonably priced—only \$4.95 each, postpaid (3 for \$14., 6 for \$24.). Add \$1.00 postage per case for orders outside U. S. Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

Jesse Jones Box Corporation (est. 1843) P. O. Box 5120 Philadelphia, Pa. 19141

Please send me, postpaid \_\_\_\_ library cases for AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY at \$4.95 each (3/\$14., 6/\$24.)

NEW SIZE $(8\frac{1}{4}" \times 11")$ 3 cases/year
OLD SIZE $(7\frac{1}{4}" \times 10\frac{1}{2}")$ copies prior to 1975
(2 cases/year)

Name		
Address		
City	State	Zip

# AJRI American Journal of Reproductive Immunology

#### Call For Papers Volume 1-1980/1981 six issues

Official Journal of The American Society for the Immunology of Reproduction and The International Coordination Committee for Immunology of Reproduction

he American Journal of Reproductive Immunology will publish reports of original human and animal research under the four subheadings of pregnancy immunology, reproductive tumor immunology, developmental immunology, and fertility immunology. The journal will also publish review papers pertinent to reproductive immunology as well as reviews of general immunologic subjects with possible applications to reproductive immunology.

The most rapid publication consistent with scientific quality and quality of production will be a major priority of

the journal, as will the rapid notification of authors of the fate of their submitted manuscripts.

Manuscripts for consideration should be submitted to the Editor-in-Chief: Norbert Gleicher, MD • Editor-in-Chief, American Journal of Reproductive Immunology • Mount Sinai Medical Center • One Gustave L. Levy Place • New York, NY 10029 • (212) 650-5980. Instructions for contributors are available from either Dr. Gleicher or the publisher.

#### SOME PAPERS TO BE PUBLISHED IN VOLUME 1

#### PREGNANCY IMMUNOLOGY

- The IgG and Transferrin Receptor of the Human Syncytiotrophoblast Microvillus Plasma Membrane, P.M. Johnson and P.J. Brown
- Cellular Immunity During Pregnancy. I. Proliferative and Cytotoxic Reactivity With Paraaortic Lymph Nodes, S.R.S. Gottesman and O. Stutman
- Cellular Immunity During Pregnancy. II. Response to T and B Cell Mitogens, S.R.S. Gottesman and O. Stutman
- Regulatory Mechanism of CMI in Allogenic Pregnancy, G. Chaouat, P. Monnot, M. Hoffman, and S. Chaffaux
- Immunology of Spontaneous Abortion and Hydatidiform Mole, S. Takeuchi
- Cyclic Pattern of Immune Responsiveness During the Estrous Cycle in Female Mice, U. Krzych, H.R. Strausser, J.P. Bressler, and A.L. Goldstein
- Protein Antigens of the Human Syncytiotrophoblast Microvillus Plasma Membrane, P.M. Johnson, A.O. Ogbimi, P.J. Brown, and L.C.P. Shah
- Fetal and Maternal Red Cell Immune Adherence (RCIA) Receptors,

  \* I. Siegel and N. Gleicher

#### Reviews

- The Biology of Immune Complexes and Their Possible Role in Pregnancy, A.N. Theofilopoulos, N. Gleicher, A.B. Pereira, and F.J. Dixon
- Histocompatibility Antigens in Pregnancy, Abortions, Infertility, Preeclampsia, and Trophoblast Neoplasms, R. Pattillo

#### **FERTILITY IMMUNOLOGY**

- The Interfering Effect of Human IgG Antisperm Antibodies on Penetration by Human Sperm of Zona-Free Hamster Eggs, G.G. Haas, Jr., D.E. Sokoloski, and D.P. Wolf
- Autoagglutination in Ejaculates Caused by Sperm-Agglutinating Antibodies, J. Friberg
- Human Soluble Antigens and Their Use in Sperm Antibody Testing, S. Shulman and T. Keane
- Studies on Local Immunity to Sperm: Dissolving of Cervical

  Mucus by Use of Bromelin With Retention of Antibody Activity,
  S. Shulman, B.A. Gray, and L. Stevens

#### DEVELOPMENTAL IMMUNOLOGY

Sequential Activation of V-Genes During Postnatal Life, C. Bona Decreased Cord Blood IgM and IgA in Trisomy, L.L. Cederqvist, S. Spigelman, and S.D. Litwin

The Fetal Lymphocyte, F. Siegal

Editor-in-Chief Norbert Gleicher

Associate Editors Lars L. Cederqvist •

Philip J. DiSaia

• Rudi Ansbacher • Hugh R.K. Barber • J.L. Beaumont • Sven Arvid Birkeland • Barry Boettcher • Constantine Bona • Christopher Chen • Carmel J. Cohen • Stanley A. Gall • Richard A. Gatti • John P. Gusdon, Jr. • Robert E. Harris • Kurt Hirschhorn • Sherman Kupfer (Consultant on Experimental Design) • Y.W. Loke • P.L. Masson • Pornchai Matangkasombut • Lilo Mettler • Jillian A. Need • Lars Olding • Roland A. Pattillo • David T. Purtilo • Chris W.G. Redman • James R. Scott • James S. Scott • Sidney Shulman • Frederick P. Siegal • Israel Siegel • Harry Smith, Jr. (Consultant on Statistical Design) • Vernon C. Stevens • Shoshichi Takeuchi • G.P. Talwar • Argyrios N. Theofilopoulos

Reproductive In \$75.00. (Addition Africa, Airspeed Send me a samp Send me instruction Payment or purchase ord	al foreign postage: Delivery, \$15.00; other ole copy of the first tions for contributo er must accompany order ge; for payments not in U.	e 1, 1980/81, six issues, Europe, Middle East, her countries, \$10.50.) issue.
City	State/Province	Zip/Postal Code
		• AJOG91580

#### INDEX TO ADVERTISERS

Baystate Medical Center	Norwich-Eaton Pharmaceuticals
Classified 40	Macrodantin 12, 13, 14
Breon Laboratories Inc.	O.T.E. Biomedica
Fergon 24	Cardiotocograph 28
Brigham Medical Associates, Inc.	Ortho Diagnostics Inc.  RhoGAM 2, 3
Classified 10	RhoGAM 2, 3
	Ortho Pharmaceutical Corporation
Genesee Health Service Medical Group  Classified 46	Ortho Novum 1/50 39 40
Cassylea 40	
	Parke-Davis Division of Warner-Lambert Company
Health Care Plan Medical Center  Classified49	Estrovis 31, 32, 33, 34
Cussylea13	Natafort 35 Norlestrin 16, 17, 18
Hoffmann-La Roche Inc.  Gantanol 36, 37, 38	Prime Health
	Classified 27
H-III P C	
Holland-Rantos Company Koromex 4	Purdue Frederick Company, The  Betadine Vaginitis Regimen 26, 27
	Detautie Vagintis Regimen 20, 27
Hospital Corporation of America	Searle Laboratories
Classified 10	Cu-7/Tatum-T Second Cover, 1
	Flagyl49, 50, Third Cover
Liss, Inc., Alan R.	
American Journal of Reproductive Immunology 47	University Associates for International Health Incorporated
	Classified 10
Louisiana State University Medical Center	
Classified 49	University of Southern California
	Classified 8
Mead Johnson Pharmaceutical Division	
Peri-Colace Fourth Cover	University of Tennessee
	Classified 46
Merck Sharp & Dohme	
Mefoxin       20, 21, 22         Urecholine       29, 30	opjoin company, the
29, 50	Cleocin Phosphate 42, 43, 44
Nowthwest Poymonante P.C.	Whitehall Laboratories
Northwest Permanente, P.C.  Classified 27	Preparation H 25

#### OB/GYN **PHYSICIAN**

OB/GYN Physician to join Health Care Plan. Opportunity for Board certified or qualified physician in innovative staff model HMO. Negotiable salary, outstanding fringe benefits, nurse-midwife, certified family practitioners, university affiliated, chance to build your own department. Position available anytime in 1980.

C.V. to Medical Director. Health Care Plan Medical Center, 120 Gardenville Parkway West. West Seneca, N.Y. 14224 or call 716-668-3600.

#### **LOUISIANA STATE** UNIVERSITY IN NEW ORLEANS

Following full-time faculty positions are available:

- 1. Director of Gynecologic Endocrinology
- 2. Director of Gynecologic Oncology
- 3. Director of Maternal-Fetal Medicine
- 4. General Obstetrician-Gynecologist
- 5. Director of program at affiliated Charity Hospital, Baton Rouge, La.

Interested applicants should send a curriculum vitae to:

Charles A. White, M.D. Professor and Head Department of Obstetrics and Gynecology L.S.U School of Medicine 1542 Tulane Avenue New Orleans, Louisiana 70112

An Affirmative Action/Equal Opportunity Employer

#### Flagy (metronidazole) 250 mg.

Metronidazole has been shown to be carcinogenic in mice and possibly carcinogenic in rats. (See Warnings.) Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the Indications section

Indications: For the treatment of symptomatic trichomoniasis in females and males when the presence of the trichomonad has been confirmed by appropriate laboratory procedures (wet smears and/or cultures). Also for the treatment of asymptomatic females when the organism is associated with endocervicitis, cervicitis, or cervical erosion. T. vaginalis infection is a venereal disease and therefore, asymptomatic sexual partners of treated patients should be treated simultaneously if the organism is present. The decision to treat an asymptomatic male partner who has a negative culture or one in whom no culture has been attempted, is an individual one. In any event, the consort should be treated with Flagyl in cases of reinfection. Flagyl is also indicated for acute intestinal amebiasis (amebic dysentery) and for amebic liver abscess

Contraindications: Evidence or history of blood dyscrasia, active organic disease of the CNS, the first trimester of pregnancy and a hypersensitivity to metronidazole.

Warnings: Flagyl should not be used in the first trimester of pregnancy (see Contraindications). Use with discretion during the second and third trimesters of pregnancy and restrict to those pregnant patients not cured by topical measures. Flagyl (metronidazole) is secreted in the breast milk of nursing mothers. It is not known whether this can be injurious to the newborn If used during lactation, an alternative method of feeding may

Tumorigenicity Studies in Rodents. Metronidazole has shown evidence of tumorigenic activity in a number of studies involving

chronic, oral administration in mice and rats.

Most prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all five reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). One of the mouse studies revealed increases in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant

In two long-term toxicity studies in the rat there was a statistically significant increase in the incidence of various neo-plasms, particularly mammary tumors, among female rats on metronidazole over that noted in the control groups

Two lifetime tumorigenicity studies in hamsters have been

reported to be negative.

Metronidazole has been reported to potentiate the anti-coagulant effect of coumarin and warfarin resulting in a pro-longation of prothrombin time. This possible drug interaction should be considered when Flagyl is prescribed for patients on this type of anticoagulant therapy.

Precautions: Mild leukopenia has been reported during Flagyl (metronidazole) use: total and differential leukocyte counts are recommended before and after treatment with the drug, especially if a second course is necessary. Flagyl may interfere with certain chemical analyses for SGOT. Avoid alcoholic beverages during Flagyl therapy because abdominal cramps, nausea, vomiting, headaches and flushing may occur. Discontinue Flagyl promptly if abnormal neurologic signs occur. Exacerbation of candidiasis may occur. In amebic liver abscess, aspirate pus during metro-nidazole therapy.

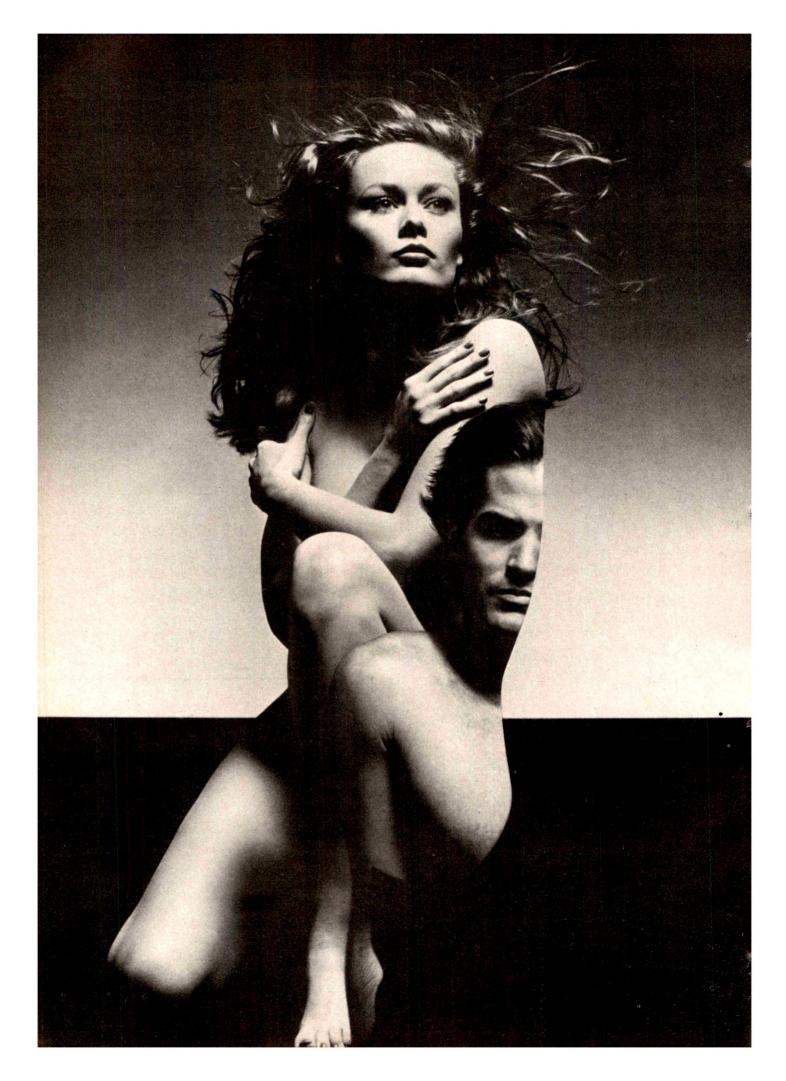
Adverse Reactions: Nausea, headache, anorexia, vomiting, diar-rhea, epigastric distress, abdominal cramping, constipation, a metallic, sharp and unpleasant taste, furry tongue, glossitis and stomatitis possibly associated with a sudden overgrowth of Candida, exacerbation of vaginal candidiasis, an occasional reversible moderate leukopenia, dizziness, vertigo, incoordination, ataxia, convulsive seizures, peripheral neuropathy, fleeting joint pains, confusion, irritability, depression, weakness, insomnia mild erythematous eruptions, urticaria, flushing, nasal congestion, dryness of the mouth, vagina or vulva, pruritus, dysuria, cystitis a sense of pelvic pressure, dyspareunia, fever, polyuria, incontinence, decrease of libido, proctitis, pyuria and darkened urine have occurred in patients receiving the drug. Patients receiving Flagyl may experience abdominal distress, nausea, vomiting, flushing or headache if alcoholic beverages are consumed. The taste of alcoholic beverages may also be modified. Flattening of the T-wave may be seen in ECG tracings.

SEARLE

Searle & Co. San Juan, Puerto Rico 00936

Address medical inquiries to: G. D. Searle & Co. Medical Communications Department, Box 5110 Chicago, Illinois 60680

941-R2 ·



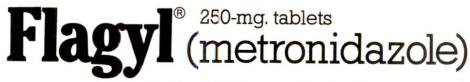
# His trichomoniasis can make her therapy useless unless they both take..

When the male is not treated for *Trichomonas vaginalis*, the female—no matter how well she cooperates with therapy—probably will become reinfected. To arrest this infection/reinfection cycle, both infected partners <u>must</u> be treated simultaneously.

The only systemic trichomonacide—In the female, trichomoniasis is a multiorgan disease. Trichomonads invade the vagina, and are often deeply entrenched in the endocervix, Skene's and Bartholin's glands, the urethra, and the bladder. The male genitourinary tract has seven possible sites of infection. Only the systemic action of Flagyl can eliminate sequestered trichomonads from these sites; topical treatments are ineffective.

**Effective in both partners**—Because it reaches infection sites via the bloodstream, Flagyl is the only trichomonacide that is effective in both men and women. And Flagyl is the only available agent of its kind.

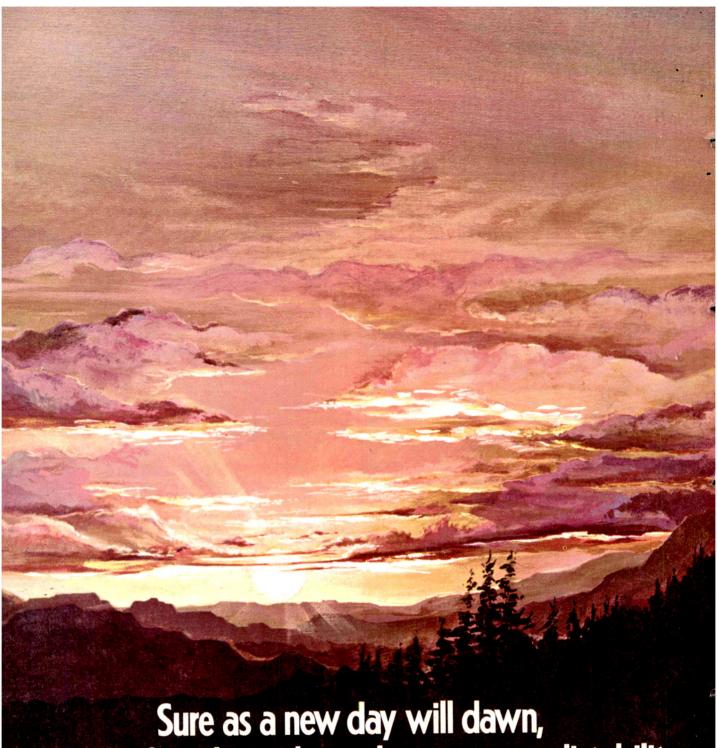
The only effective trichomonacide for couples



Please see adjacent page for brief summary of prescribing information.



Address medical inquiries to: G.D.Searle & Co. Medica Communications Department, Box 5110 Chicago, Illinois 60680



# Peri-Colace works with gentle, proven predictability

PERI-COLACE combines the gentle laxative and effective stool softener so often needed when bowel motility is depressed. PERI-COLACE acts gently to induce peristalsis, while the stoolsoftening agent lets natural intestinal water permeate stools.

PERI-COLACE is predictable—gentle evacuation usually occurs within 8 to 12 hours. It is useful in obstetrical patients, as well as in geriatrics, preand postoperative patients, the convalescent, in patients with medicationrelated suppression of bowel motility and children.

PERI-COLACE -gentle, proven, pre-

Gentle laxative plus stool softener

PHARMACEUTICAL DIVISION

October 1, 1980 volume 138, number 3

# American Journal OBSTETRICS AND GYNECOLOGY

Copyright @ 1980 by The C. V. Mosby Company

Editor in Chief
JOHN I. BREWER

Editors

FREDERICK P. ZUSPAN · E. J. QUILLIGAN

Associate Editor

Emeritus Editors
HOWARD C. TAYLOR, JR. · ALLAN C. BARNES

#### Official Publication

AMERICAN GYNECOLOGICAL SOCIETY

AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA

SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

PACIFIC COAST OBSTETRICAL AND GYNECOLOGICAL SOCIETY

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

SOCIETY FOR GYNECOLOGIC INVESTIGATION

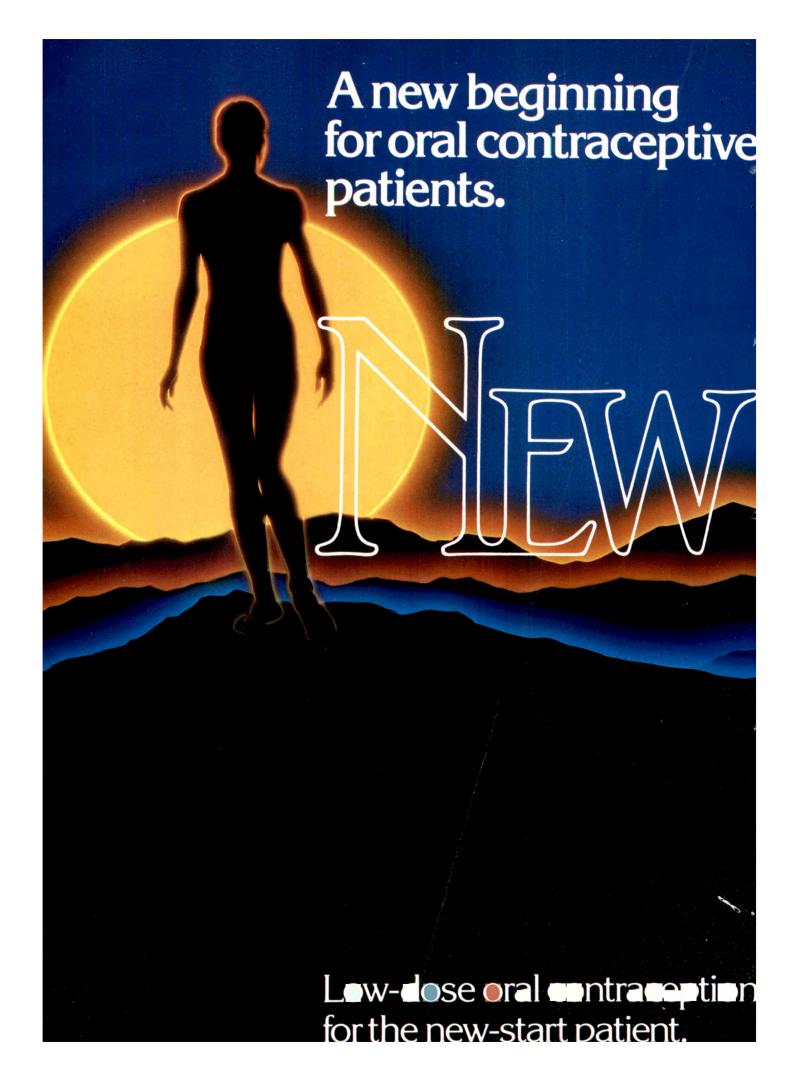


Published by

THE C. V. MOSBY COMPANY St. Louis, Missouri 63141



ISSN 0002-9378



#### Now—a refinement in low-dose oral contraception.

New Norinyl 1+35 from Syntex was specifically formulated to satisfy the goals of effective low-dose contraception, while reducing the possibility of commonly encountered side effects such as breakthrough bleeding.

Norinyl 1+35 contains 1.0 mg of norethindrone—the time-tested progestin...and 0.035 mg of ethinyl estradiol—a well accepted level of estrogen.

This level of norethindrone serves two important functions. First, it helps insure a high rate of efficacy. Secondly, it reduces the possibility of breakthrough bleeding.

#### An unsurpassed rate of efficacy.

No pregnancies have been reported with Norinyl 1-when it has been taken as directed. In fact, its efficient is comparable to that achieved with higher-off formulations.<sup>†</sup>

#### With little chance of breakthrough bleeding

Norinyl 1+35 provides sufficient endometrial supportion assure comfortable contraception for the vast major women—with very little likelihood of breakthrobleeding.

# Tablets (norethindrone 1.0 mg and ethinyl estradiol 0.035 mg)



<sup>\*</sup>Note: serious as well as minor side effects have been reported following th use of all oral contraceptives. These include thromboembolic disease. Pleas see summary of Prescribing Information on following page.

<sup>†</sup>The overall pregnancy rate was 0.17 per hundred woman-years, in clinical trials with 940 patients completing 14,366 cycles of use.

Norinyl\* 1+35 21-Day Tablets (norethindrone 1 mg. with ethinyl

Norinvi\* 1+35 28-Day Tablets (21 norethindrone 1 mg. with ethiny

#### ORAL CONTRACEPTIVE (O.C.) AGENTS

Indications O.C.s are indicated for the prevention of pregnancy. DOSE RELATED RISK OF THROMBOEMBOLISM FROM O.C.s. Studies have shown a positive association between the dose of estrogens in O.C.s and the risk of thromboembolism. For this reason, it is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The O.C. prod thromboembolism. For this reason, it is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The O.C. product prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance. It is recommended that new acceptors of O.C.s should be started on preparations containing 0.05 mg or less of estrogen. Contraindications 1. Known or suspected pregnancy (see Warning No. 5). 2. Thrombophiebits or thromboembolic disorders. 3. A past history of deep vein thrombophiebits or thromboembolic disorders. 3. A past history of deep vein thrombophiebits or thromboembolic disorders. 4. Undiagnosed abnormal genital bleeding. 5. O.C.s should not be used by women who have or have had any of the following conditions: a. Cerebral vascular or coronary arthry disease. b. Known or suspected carcinoma of the breast. c. Known or suspected estrogen dependent neoplasia. d. Benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen containing products.

WARNINGS: Cigarette smoking increases the risk of serious car-diovascular side effects from 0.C. use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use 0.C.s should be strongly advised not to smoke.

The use of 0. C.s is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, liver tumor, gall bladder disease, visual disturbances, fetal abnormalities, and hypertension. Practitioners prescribing 0.C.s should be familiar with the following information relating to these risks.

The use of 0.C.s is associated with increased risk of several serious conditions including thrombembolism. Stroke, myocardial infarction, investiment, and hypertension. Practitioners prescribing 0.Cs should be familiar with the following information relating to these risks.

1. Thrombembolic Diorders and Other Vascular Problems: An increased risk of thromboembolic and thrombotic disease associated with the use of 0.C.s is well established. One Britishs tude in the large of the risk for increased relationship of the risk of the risk of the risk for increased relationship of the risk of th

ible 1. The annual number of deaths associated with control of fertility and a control per 100,000 nonsterile women by regimen of control and age of

		15-19	20-24	25-29	30-34	35-39	40-44
o method		5.6	6.1	7.4	13.9	20.8	22.6
portion only		1.2	1.6	1.8	1.7	1.9	1.2
II only -nonsmokers		1.3	1.4	1.4	2.2	4.5	7.1
Il only -smokers		1.5	1.6	1.6	10.8	13.4	58.9
Ds only aditional		0.9	1.0	1.2	1.4	2.0	1.9
ntraception only	•	1.1	1.6	2.0	3.6	5.0	4.2
ption and abortion		0.2	0.2	0.3	0.3	0.3	0.2

e risk of thromboembolic and thrombotic disease associated with O.C.s. reases with age after approximately age 30 and, for myocardial infarction, further increased by hypertension, hypertipidemias, obesity, diabetes or story of preeclampic toxemia and especially by cigarette smoking. Based on

the data currently available, the following table gives a gross estimate of the risk of death from circulatory disorders associated with the use of 0.C.s.: **Table 2.** Smoking habits and other predisposing conditions—risk associated with use of 0.C.s.

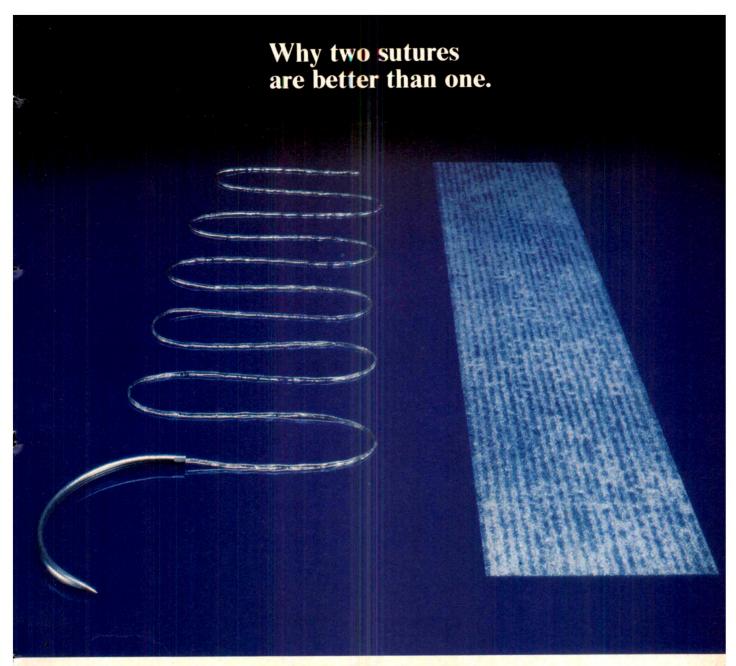
Age	Below 30	30-39	40+
Heavy smokers Light smokers Nonsmokers	C	B	A B
(No predisposing conditions) Nonsmokers	D	C,D	С
(other predisposing conditions)	C	C,B	B,A
A—Use associated with very high risk. B—Use associated with high risk.	C — Use associ D — Use associ	ated with mo	derate risk.

B—Use associated with high risk.

D—Use associated with nigh risk.

The physician and the patient should be altert to the actient smitistations of thromboemboic and thrombotic disorders (e.g., thromboemboils, pulmary ambibilism, cerebrovascian insufficiency, coronary occlusion, retinal thromboems, and mesenteric thrombosis. Should any of these occur or be increased risk of post-surgery of a year sociated with an increased risk of superful superful ported in O.C. users. If feasible, O.C.s should be discontinued at least 4 weeks before surgery of a year seasociated with an increased risk of thromboembolism or prolonged immolitism. Data also suggest that the present produce of the leg, the patient of the property of the property of the property of the property of the leg, the patient of the property of the property of the leg, the leg

pregnancy. 6. Gail Bladder Dissase: Studies report an increased risk of gail bladder disease in users of Q.C.s. or estorgens. In one study, an increased risk appeared after 2 years of use and doubled after 4 of 5 years of use. In user, 2 or 2 of 12 of



Steri-Strip\* Skin Closures are tape sutures which can be used with traditional sutures to provide important advantages for you and your patients.

Use of Steri-Strip Skin Closures results in better cosmetic appearance, greater patient comfort, minimal tissue trauma and less infection potentiation due to excellent porosity, while providing long term wound support.

3M Steri-Strips can be applied quickly and easily and may be used alone, with subcutaneous or subcuticular sutures or in conjunction with percutaneous sutures.



Pfannenstiel incision closed with subcutaneous sutures and Steri-Strip Skin Closures



The incision site 17 days post-operative

For further information, contact your 3M Surgical Products sales representative.

#### Surgical Products Division/3M

3M Center, St. Paul, MN 55144

		FREE Steri-Stri Strip Sample Ki	
Name			
Hospital		No. 0	of Beds _
Address	(To assure deliv	ery, be sure to give	hospital add
City	(10 assure denv	State	
Telephone Nu	ımber (	)	Zip -
3M Center	gical Products St. Paul, MN rson • Good only i		

OBG-005



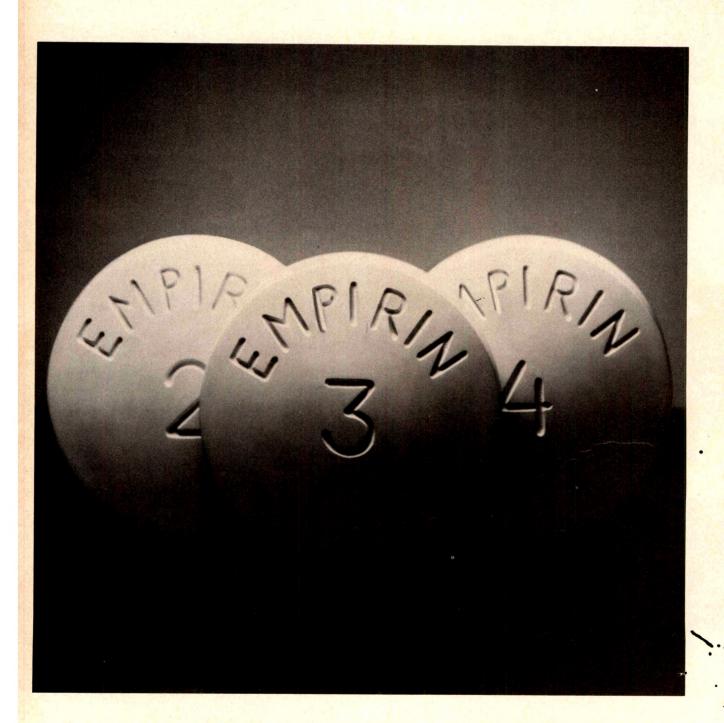
#### AS CLOSE AS A CLASSIC CAN COME TO THE FUTURE.

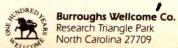
Aspirin and codeine. Classic agents whose respective roles in medicine continue to be developed. Empirin® C Codeine. An impressive history and an important future.

## EMPIRIN' T CODEINE

Each tablet contains: aspirin, 325 mg; plus codeine phosphate in one of the following strengths: No. 2—15 mg, No. 3—30 mg, and No. 4—60 mg. (Warning—may be habit-forming.)







#### American Journal of Obstetrics and Gynecology

**Contents** 

Copyright © 1980 by The C. V. Mosby Company

#### October 1

(Contents continued on page 7)

1980

#### **Obstetrics**

Bedford Park, South Australia

Outcome of pregnancy in sickle cell anemia and sickle cell-hemoglobin C diseas	se 239
Paul F. Milner, M.D., Bennie R. Jones, L.P.N., and Johanna Döbler, B.Sc.	
Augusta, Georgia	
Analysis of heart rate and beat-to-beat variability: Interval difference index	246
Herman P. van Geijn, M.D., Ph.D., Henk W. Jongsma, Ph.D., Jelte de Haan, M.D., Ph.D.,	
and Tom K. A. B. Eskes, M.D., Ph.D.	
Nijmegen, The Netherlands	
Pregnancy-specific $\beta_1$ -glycoprotein as a prognostic indicator in complications of	253
early pregnancy	
P. C. Ho, M.B., B.S., M.R.C.O.G., and W. R. Jones, M.D., Ph.D., F.R.C.O.G.	

Vol. 138, No. 3, October 1, 1980. The American Journal of Obstetrics and Gynecology is published semimonthly by The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141. POSTMASTER: Send address changes to above address.

1980 Annual subscription rates	U.S.A.	Foreign countries (surface mail) All regions	Region 1	Foreign countries (airmail)* Region 2	Region 3
Institutional† Individual‡ Student, resident‡	\$52.50	\$72.50	\$101.45	\$132.65	\$163.85
	\$35.50	\$55.50	\$ 84.45	\$115.65	\$146.85
	\$28.40	\$48.40	\$ 77.35	\$108.55	\$139.75

Single copies are \$4.50 postpaid. Remittances should be made by check, draft, or post office or express money order, payable to this Journal.

\*Airmail breakdown—Domestic: First-class and Priority rates for the U.S. and possessions are available upon request. Region 1: Central America, islands, and mainland colonies of European countries in The Americas. Region 2: South America, Europe, Egypt, Africa (bordering the Mediterranean). Region 3: Asia, Australasia, Africa (other than Mediterranean), Middle East, Far East, The Pacific, U.S.S.R. (and constituent Republics).

†Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics; city, county, state, provincial, and national government bureaus and departments; and all commercial and private institutions and organizations.

‡Personal subscriptions and all student-rate subscriptions must be in the names of, billed to, and paid by individuals. All student-rate requests must indicate training status and name of institution.

Subscriptions may begin at any time.

Second-class postage paid at St. Louis, Missouri, and additional mailing offices. Printed in the U.S.A. Copyright © 1980 by The C. V. Mosby Company.

#### T'S YOUR CHOICE for Laparoscopy from Karl Storz with HOPKINS Telescope PEDIATRIC SINGLE PUNCTURE LAPAROSCOPE PEDIATRIC DOUBLE PUNCTURE LAPAROSCOPE Telescope, 2.7 mm O.D. Telescope, 4 mm O.D.; Trocar and Cannula, 4.5 mm O.D., uninsulated Trocar and Cannula 5.5 mm O.D., uninsulated, as shown 6.5 mm O.D., insulated (not shown) SINGLE PUNCTURE LAPAROSCOPE Telescope, 6.5 mm O.D. Trocar and Cannula 11 mm O.D., uninsulated, as shown 12 mm O.D., insulated (not shown) DOUBLE PUNCTURE LAPAROSCOPE Telescope, 6.5 mm O.D.; Trocar and Cannula, 7 mm O.D., uninsulated **OPERATING LAPAROSCOPE, PARALLEL VIEWING** Telescope, 10.5 mm O.D. Trocar and Cannula 11 mm O.D., uninsulated, as shown 12 mm O.D., insulated (not shown) **OPERATING LAPAROSCOPE** Telescope, 10.5 mm O.D. Trocar and Cannula 11 mm O.D., uninsulated, as shown 12 mm O.D., insulated (not shown) A Tradition of Leadership in Craftsmanship and Design \*Invention of Prof. H. H. Hopkir Karl Storz Endoscopy-America, Inc. 658 South San Vicente Blvd., Los Angeles, Ca. 90048 Name (please print) FOR TOLL FREE SERVICE . 800-421-0837 (Except California) In California CALL (213) 651-1068 Address

City

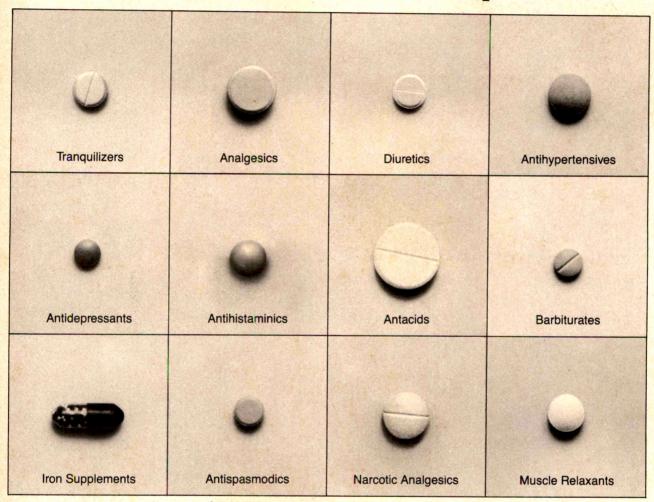
State

Please send me further information. 
Please have a Karl Storz Representative phone me for an appointment.

#### Contents continued from page 5

Contents commune nom page s	of Salesee
Copper and ceruloplasmin activity in human amniotic fluid	257
Wai-Yee Chan, Joann Richichi, Guy E. Griesmann, William Cushing, O. Ray Kling, and Owen M. Rennert	
Oklahoma City, Oklahoma	
Epidural morphine analgesia in second-trimester induced abortion	260
Florella Magora, M.D., Y. Donchin, M.D., D. Olshwang, M.D., and J. G. Schenker, M.D. Jerusalem, Israel	
Hemodynamics in patients with severe toxemia during labor and delivery	263
Terence D. Rafferty, M.D., and RIchard L. Berkowitz, M.D.  New Haven, Connecticut	
Stable prolactin level after enhanced estradiol production following dehydroepiandrosterone sulfate	271
A. Kauppila, M.D., and O. Ylikorkala, M.D.  Oulu, Finland	
Fetus, placenta, and newborn	
Morphologic and histochemical evidence for the occurrence of collagenolysis and	273
for the role of neutrophilic polymorphonuclear leukocytes during cervical dilation	
L. C. U. Junqueira, M. Zugaib, G. S. Montes, O. M. S. Toledo, R. M. Krisztán, and	
K. M. Shigihara São Paulo, Brazil	
Effects of maternal cigarette smoking on fetal breathing and fetal movements	282
I. Thaler, M.D., J. D. S. Goodman, M.B., M.R.C.O.G., and	
G. S. Dawes, D.M., F.R.C.O.G., F.R.S.  Oxford, England	
Time-lapse study of normal human trophoblast in vitro	288
Judith Lueck, B.S., and Silvio Aladjem, M.D.	
Chicago and Maywood, Illinois	
Maternal and fetal immune responses to human trophoblast antigens	293
Pamela V. Taylor  Leeds, England	
Ultrasound measurement of fetal limb bones	297
John T. Queenan, Gregory D. O'Brien, and Stuart Campbell	
London, England	222
Possible acceleration of neurological maturation following high-risk pregnancy  Claudine Amiel-Tison	303
Paris, France	
(Contents continued	on page 9)

# Til Constip to s Many of the drugs you prescribe may also cause constipation



#### Relieve drug-induced constipation

# SENOKOT®

(standardized senna concentrate)

#### natural vegetable laxative

- Senokot laxatives help alleviate constipation in patients taking certain constipating drugs.
- Virtually colon-specific action.
- Flexible, individualized dosage.
- effective relief or prevention of druginduced constipation in 98% of 621 patients reported in 7 studies.\*

\*Bibliography on request

#### **Purdue Frederick**

© Copyright 1980, The Purdue Frederick Company/Norwalk, CT 06856

#### **Gynecology**

Technical failures in tubal ring sterilization: Incidence, perceived reasons,	307
outcome, and risk factors	
I-cheng Chi, M.D., Dr.P.H., Stephen D. Mumford, Dr.P.H., and Leonard E. Laufe, M.D.	
Research Triangle Park, North Carolina	
Trophoblastic disease monitoring: Evaluation of pregnancy-specific	313
$\beta_1$ -glycoprotein	
Timothy J. O'Brien, Eva Engvall, J. B. Schlaerth, and C. Paul Morrow	
Los Angeles and La Jolla, California	
Vaginal intraepithelial neoplasia: Biologic aspects and treatment with topical	321
5-fluorouracil and the carbon dioxide laser	
Edmund S. Petrilli, M.D., Duane E. Townsend, M.D., C. Paul Morrow, M.D., and	
Calvin Y. Nakao, M.D.	
Los Angeles, California	
Granulosa cell tumors: A comparison of survival in patients and matched controls	329
Elisabet Björkholm, M.D.	
Stockholm, Sweden	
Evidence for a human ovarian progesterone receptor	332
Barry R. Jacobs, M.D., Susan Suchocki, and Roy G. Smith, Ph.D.	
Houston, Texas	
Relaxation of human female genital sphincters by the neuropeptide vasoactive	337
intestinal polypeptide	
B. Walles, Ph.D., R. Håkanson, Ph.D., G. Helm, M.D., Ch. Owman, M.D., Ph.D.,	
NO. Sjöberg, M.D., Ph.D., and F. Sundler, Ph.D.	
Lund, Sweden	
The double uterus associated with an obstructed hemivagina and ipsilateral renal agenesis	339
John A. Rock, M.D., and Howard W. Jones, Jr., M.D.	
Baltimore, Maryland	

#### Communications in brief

### Streptococcus sanguis sepsis and meningitis: A complication of vacuum extraction Richard E. Heath, Jr., M.D., Jack A. Rogers, Jr., M.D., Lawrence V. Cheldelin, M.D., and

Richard E. Heath, Jr., M.D., Jack A. Rogers, Jr., M.D., Lawrence V. Cheldelin, M.D., and Allen P. Killam, M.D.

El Paso, Texas



### We put our milk on a diet for you.

You can even mix it thick and it won't get fat. That's because we took the fat out. Yet we kept the protein, calcium and B-vitamins, and fortified Carnation Instant Nonfat Dry Milk with vitamins A and D.

Since our milk starts out dry, you can control the balance of protein and solids to suit any low-fat diet. To illustrate, we've prepared free diet plans for your patients. Each diet plan booklet has 12 identical, tear-out patient plans with general instructions, a basic meal plan and a sample menu. There's even a column for your special notes.

·Circle the numbers of the free diet

plans you want and send us the coupon: 1. Pregnancy Weight Control.

- 2. Reducing. 3. Cholesterol Control.
- 4. Hypoglycemia. 5. Low Sodium.
- 6. Bland Ulcer. 7. Diabetic.

Send me the following free plans $-1-2-3-4-5-6-7$ (circle appropriate number)
Send to:
Carnation Company, P.O. Box 550,
Dept. 0D, Pico Rivera, Calif. 90665
NAME
ADDRESS
CITY

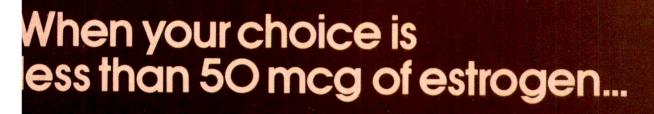
#### Contents continued from page 9

Sources of error in the estimation of fetal gestational age	344
Ivan E. Zador, Ph.D., Roger H. Hertz, M.D., Robert J. Sokol, M.D., and	
Victor J. Hirsch, B.S.	
Cleveland, Ohio	
	345
Estimation of success in treatment of premature labor: Applicability of	
prolongation index in a double-blind, controlled, randomized trial	
L. L. Penney, M.D., and W. C. Daniell, M.D.	
El Paso, Texas	
Hematocolpometra in the presence of normal menstruation	346
Terrance S. Drake, Commander, MC, USN, F.A.C.O.G., and	
William F. O'Brien, Lieutenant Commander, MC, USNR	
Bethesda, Maryland	
Fatal influenzal pneumonia in pregnancy: Failure to demonstrate transplacental	347
transmission of influenza virus	
Reuben Ramphal, M.D., William H. Donnelly, M.D., and Parker A. Small, Jr., M.D.	
Gainesville, Florida	
Ganesvine, Florida	348
Abdominal sacral colpopexy	340
W. Cowan, M.D., F.R.C.S.(C.), and H. R. Morgan, M.D., F.R.C.S.(C.), F.A.C.O.G.	
Hamilton, Ontario, Canada	
Benign glandular inclusions in para-aortic lymph nodes: A cause for false positive	350
lymphangiography	
Volker Schneider, M.D., James W. Walsh, M.D., and Dean R. Goplerud, M.D.	
Richmond, Virginia	
	351
Human pasteurellosis: The first reported case of Pasteurella multocida septicemia	
and peritonitis during pregnancy	
Wing K. Kam, M.D., Ph.D., Harry W. Haverkos, M.D., Harvey M. Rodman, M.D.,	
Ralph Schmeltz, M.D., and David H. Van Thiel, M.D.  Pittsburgh, Pennsylvania, and Cleveland, Ohio	
	050
Hysterosalpingography in young infertile patients with unsuspected endometrial adenocarcinoma	352
Joseph Menczer, M.D., Yair Frenkel, M.D., and David M. Serr, M.D.	
Tel-Hashomer and Tel-Aviv, Israel	
Items	
	The True of the last

Items 354

Information for authors on page 21

Index to advertisers on page 46



# Ortho-Novum 1/35

ach peach tablet contains 1.0 mg norethindrone and 0.035 mg ethinyl estradiol. ach green tablet in the 28-day regimen contains inert ingredients.

# a trusted progestogen:

An established level of norethindrone, with 23,000,000 woman-years of clinical experience.

# a trusted estrogen level:

35 mcg ethinyl estradiol provides a low estrogen level in a combination chosen by computer analysis of clinical data.

Highly effective—no pregnancies occurred in clinical studies when taken as directed.

Overall pregnancy rate of 0.17 per 100 woman-years in clinical trials involving 940 women completing 14,366 cycles.

An estrogen/progestogen combination with a low incidence of amenorrhea and breakthrough bleeding †

During clinical trials, Ortho-Novum 1/35 consistently demonstrated support of endometrial integrity, with breakthrough bleeding approaching rates of 50 mcg products.

Available in 21- and 28-day regimens in the unique Dialpak\* tablet dispenser



\*Trademark

†Serious as well as minor side effects have been reported with the use of oral contraceptives. These include thromboembolic disease. The physician should remain plat to the earliest manifestations of any symptoms of serious disease.



Please see Complete Prescribing Information, a brief summary of which appears on the next page.

ORTHO

#### ORTHO-NOVUM\* 1/35 Tablets

IMPORTANT NOTE—This information is a BRIEF SUMMARY of the complete prescribing information provided with the product and therefore should not be used as the basis for prescribing the product. This summary was prepared by deleting from the complete prescribing information certain text, tables, and references. The physician should be thoroughly familiar with the complete prescribing information and patient information before prescribing the product.

INDICATION: CONTRACEPTION. The pregnancy rate in women using conventional combination oral contraceptives (containing 35 mig or more of ethinyl estradiol or 50 mig or more of mestranol) is generally reported as less than one pregnancy per 00 woman-years of use. Sightly higher rates (somewhat more than one pregnancy per 100 woman-years of use) are reported for some combination products containing 35 mig or less of ethinyl estradiol, and rates on the order of three pregnancies per 100 woman-years are terported for the progestogen-only oral contraceptives. Table 1 gives ranges of pregnancy rates reported in the literature for other means of contraception. The efficacy of these means of contraception. Table 1: Pragnancies Per 100 Woman-Years. IUD, less than 1-6. Disphragm with spermicidal product (creams or jellies), 2-20, clondom, 3-63. Aerosol foans, 2-29. Jellies and creams, 4-36. Periodic abstinence (rhythmi) all types, less than 1-47. I Calendar method, 1-47; 2. Lemperature method, 1-20, 3. Temperature method—intercourse only in postovitory phase. Less than 1-77; 4. Mucus method, 1-25, No contraception, 60-80. 005c-RELATED RISK 0F THROMBOCHBOUISM FROM DRALL CONTRACEPTIVES: Two studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. For this reason, it is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The roal contraceptive product prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance. It is recommended that new acceptors of oral contraceptive sets a started on preparations containing, 05 mg or les destr

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking [15 or more cigarettes per day] and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke. The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism stroke, myocardial infarction, hepaitc adenoma, gallbladder disease, hyperfension. Practitioners prescribing eral contraceptives should be familiar with the following information relating to these risks.

spet. Women who use oral contraceptives is associated with increased risk of several serious conditions including thromboemboliss article. myocardial infarction, hepatic adenose, galibhader disease, hyperfession. Practitioners prescribing vari contraceptives in the service.

1. THROMBOEMBOULD DISGROERS AND OTHER WASCULAR PROBLEMS. An increased risk of thromboembolic and thromboembolic disease associated with the use of oral contraceptives is well established. Four principal studies in Great Britain and both hemorrhagic and thromboembolic. These studies meased risk of tall and nondatal venous thromboembolism and stroke, the new properties of the service of th

SMOKING HABITS AND OTHER PREDISPOSING CONDITIONS—RISK ASSOCIATED WITH USE OF ORAL CONTRACEPTIVES

Age	Below 30	30-39	40+	
Heavy smokers	С	В	A	A-Use associated with very high risk.
Light smokers	D	C	В	B-Use associated with high risk:
Nonsmokers (no predisposing conditions)	D	C.D	C	C-Use associated with moderate risk.
Nonsmokers (other predisposing conditions)	C	C.B		D-Use associated with low risk

Figure 1. Estimated annual number of deaths associated with control of fertility and no control per 100,000 nonsterile

world, by regimen or control and age of wor	man. 15-19	20-24	25-29	30-34	35-39	40-44
No method	5.5	5.2	7.1	14.0	19.3	21.9
Abortion only	2.3	2.5	2.5	5.2	9.8	
Pill only-nonsmokers	1.3	1.4	1.4	2.2	4.5	6.6
Pill only-smokers	1.5	1.6	1.6	10.8	13.4	58.9
IUDs only	1.1	1.2	1.2	1.4	1.6	1.4
Traditional contraception only	1.1	1.4	1.9	3.7	4.7	4.0
Traditional contraception and abortion	0.3	0.4	0.4	0.8	14	0.8

Apartino only

2.5 | 2.7 | 1.1 | 1.4 | 1.5 | 2.5 | 2.8 | 8.6 |
Pill only-ambiest

1.5 | 1.5 | 1.5 | 1.5 | 2.5 | 2.8 | 8.6 |
Pill only-ambiest

1.5 | 1.5 | 1.5 | 2.5 | 2.8 | 8.6 |
Pill only-ambiest

1.5 | 1.5 | 1.5 | 2.5 | 2.8 | 8.6 |
Pill only-ambiest

1.5 | 1.5 | 1.5 | 2.5 | 2.8 | 8.6 |
Pill only-ambiest

1.5 | 1.5 | 1.5 | 2.5 | 2.8 | 8.6 |
Pill only-ambiest

1.5 | 1.5 | 2.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 1.5 | 2.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 2.5 | 8.6 |
Pill only-ambiest

1.5 | 2.5 | 8.6 |
Pill

#### **Editors**

JOHN I. BREWER, Editor in Chief

FREDERICK P. ZUSPAN, E. J. QUILLIGAN, Editors

ALBERT B. GERBIE, Associate Editor

HOWARD C. TAYLOR, JR., ALLAN C. BARNES, Emeritus Editors

#### Advisory committee on policy

C. D. Christian

Leo J. Dunn

George D. Malkasian

David Figge

Roy T. Parker

W. Ann Reynolds

A. Brian Little

J. C. G. Whetham

#### Board of corresponding editors

Oscar Aguero, Caracas
Frederick Kubli, Heidelberg
Pierre O. Hubinont, Brussels
Malcolm Symonds, Nottingham
Ichiro Taki, Fukuoka



# **If she** could cope, she wouldn't have called.

### **Vasomotor**

The severity of vasosymptoms motor symptoms is notoriously variable.

So is the individual patient's reaction to them. What is viewed as a passing annoyance by one may be incapacitating to another.

When should estrogen replacement therapy be initiated?

First, moderate to severe flushes and sweats are a good indicator. But in addition, consider the problem that brought her to you in the first place: her ability to cope with these vasomotor symptoms—or, more accurately, the lack of her

ability to cope. Finally, determine the absence of contraindications to estrogen therapy. For these women the high rate of effectiveness

of PREMARIN (Conjugated Estrogens Tablets. U.S.P.) against vasomotor symptomatology remains unchallenged.

In most cases the patient who should be helpe can be helped — with careful attention to dosag regimen, and follow-up—until the period of physiologic adjustment to low endogenous estrogen levels is complete.

PREMARIN.

The proven therapy many women need.

Vasomotor symptoms beyond counseling... well within the reach of

**PREMARIN** (CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg/0.625 mg/1.25 mg/2.5 mg

#### ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF

1.ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. 1-3 This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. 1 The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment? and on estrogen dose. 3 In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration. 3 it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANOY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. In sirisk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis. It is not known whether they are precursors of malignancy, Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. In infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy or in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation. 2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

**DESCRIPTION:** PREMARIN (Conjugated Estrogens Tablets, U.S.P.) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and  $17\alpha$ -dihydroequilin, together with smaller amounts of  $17\alpha$ -estradiol, equilenin, and  $17\alpha$ -dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences – National Research Council and/or other information, FDA has classified the cations for use as follows:

1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis.

- Kraurosis vulvae
- Female hypogonadism
   Female castration.
   Primary ovarian failure.
- Breast cancer (for palliation only) in appropriately selected women and men with

7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.

8. Prostatic carcinoma—palliative therapy of advanced disease.

9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens. PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning) 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

malignancy).

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast. \*\* although a recent study has raised this possibility.\*\* There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens. \*\*

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engagement, these been used to treat prostatic or breast cancer or postpartum breast engagement, these been

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. 19-22 Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. 23-30 Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. 31,32 An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. 33-34 If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophiebitis, thromboembolic disorders or in persons with a history of such disorders in association with

artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown 15 to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a

clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. In Increased blood pressure may occur with use of estrogens in the menopause. In an ablood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be

cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete. The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.
b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
d. Impaired glucose tolerance.
e. Decreased prepanediol excretion.

d. Impaired glucose tolerance.
e. Decreased pregnanediol excretion.
f. Reduced response to metyrapone test.
g. Reduced serum folate concentration.
h. Increased serum friglyceride and phospholipid concentration.
As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome, amenorrhea during and after treatment; increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair, hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido

chorea; increase or decrease in weight; reduced carbonydrate tolerance; aggravation of porphyria; edema; changes in libido

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION: 1. Given cyclically for short term use only. For treatment of moderate to severe vasomotor symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. Given cyclically: Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis

2 Given cyclically: Female hypogonadism. Female castration. Primary ovarian failure. Osteoprosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same cosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium. If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. Given for a few days: Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg daily, cyclically: lacenarically: Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal yaquing blacking.

Patients with an intact ulerus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each purple tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each yellow tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867—Each red tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868—Each green tablet contains 0.3 mg in bottles of 100 and 1,000.

PHYSICIAN REFERENCES: 1 Ziel, H.K., et al.: N. Engl. J. Med. 293:1167-1170, 1975. 2 mith, D.C., et al.: N. Engl. J. Med. 293:1164-1167, 1975. 3. Mack, T.M., et al.: N. Engl. J. Med. 294:1262-1267, 1976. 4. Weiss, N.S., et al.: N. Engl. J. Med. 294:1259-1262, 1976. 5. Herbst, A.L., et al.: N. Engl. J. Med. 284:878-881, 1971. 6. Greenwald, P., et al.: N. Engl. J. Med. 285:390-392, 1971. 7. Lanier, A., et al.: May Clin. Proc. 487:93-799, 1973. 8. Herbst, A., et al.: Obstet. Gynecol. 40:287-298, 1972. 9. Herbst, A., et al.: Am. J. Obstet. Gynecol. 18:607-615, 1974. 10. Herbst, A., et al.: N. Engl. J. Med. 292:334-339, 1975. 11. Staff, A., et al.: Obstet. Gynecol. 48:118-128, 1974. 12. Sherman, A.L., et al.: Chostet. Gynecol. 48:513-545, 1974. 13. Gal. I., et al.: Nature 216:83, 1967. 14. Levy, E.P., et al.: Lancet 1:611, 1973. 15. Nora, J. et al.: Lancet 1:414-1942, 1973. 16. Janench. D.T., et al.: N. Engl. J. Med. 296:87-700, 1974. 17. Boston Collaborative Drug Surveillance Program: N. Engl. J. Med. 296:77-700, 1974. 18. Hoover, R., et al.: N. Engl. J. Med. 295:401-405, 1976. 19. Daniel. D. G., et al.: Lancet 1:267-279, 1967. 23. Royal College of General Practitioners: J.R. Coil. Cancer 26:249-256, 1970. 23. Royal College of General Practitioners: J.R. Coil Contraceptives and Health, New York, Pitman Corp., 1974. 24. Inman, W.H.W., et al.: Br. Med. J. 2:193-199, 1968. 25. Vessey, M.P., et al.: Br. Med.

J.A.M.A. 214:1303-1313, 1970 36. Mays, E.T., et al.: J.A.M.A. 235 730-732, 1976. 37 Pfeffer, R.I.

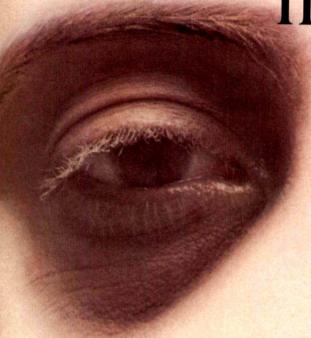
#### American Journal of Obstetrics and Gynecology

in addition to those listed on the front cover the Journal is the official publication of the following societies

NEW YORK OBSTETRICAL SOCIETY OBSTETRICAL SOCIETY OF PHILADELPHIA BROOKLYN GYNECOLOGICAL SOCIETY ST. LOUIS GYNECOLOGICAL SOCIETY NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY THE OBSTETRICAL AND GYNECOLOGICAL SOCIETY OF MARYLAND CHICAGO GYNECOLOGICAL SOCIETY CINCINNATI OBSTETRICAL AND GYNECOLOGICAL SOCIETY WASHINGTON GYNECOLOGICAL SOCIETY PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY BOSTON OBSTETRICAL SOCIETY LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY SEATTLE GYNECOLOGICAL SOCIETY ALABAMA ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS AKRON OBSTETRICAL AND GYNECOLOGICAL SOCIETY KANSAS CITY GYNECOLOGICAL SOCIETY CENTRAL NEW YORK ASSOCIATION OF GYNECOLOGISTS AND OBSTETRICIANS

NEW JERSEY OBSTETRICAL AND GYNECOLOGICAL SOCIETY IOWA OBSTETRIC AND GYNECOLOGIC SOCIETY THE TEXAS ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS OKLAHOMA CITY OBSTETRICAL AND GYNECOLOGICAL SOCIETY MEMPHIS OBSTETRICAL AND GYNECOLOGICAL SOCIETY UTAH OBSTETRICAL AND GYNECOLOGICAL SOCIETY ROCHESTER OBSTETRICAL AND GYNECOLOGICAL SOCIETY ARKANSAS OBSTETRICAL AND GYNECOLOGICAL SOCIETY TENNESSEE STATE OBSTETRICAL AND GYNECOLOGICAL SOCIETY NEW YORK GYNECOLOGICAL SOCIETY PACIFIC NORTHWEST OBSTETRICAL AND GYNECOLOGICAL ASSOCIATION BUFFALO OBSTETRICAL AND GYNECOLOGICAL SOCIETY SAN FRANCISCO GYNECOLOGICAL SOCIETY JACKSON GYNECIC SOCIETY INDIANA OBSTETRICAL AND GYNECOLOGICAL SOCIETY THE MINNESOTA OBSTETRICAL AND GYNECOLOGICAL SOCIETY

# SOME PEOPLE CLAIM THEY WERE BORN TIRED.



### IRON-DEFICIENCY ANEMIA MAY MAKE THEM FEEL THAT WAY.

For patients with iron-deficiency anemia,
Tabron provides 100 mg of elemental iron\* in a single tablet daily—enough to produce a clinically significant hemoglobin response.

General fatigue and lassitude are common presenting symptoms of the anemic patient. So when the patient complains about how difficult it has become to carry out normal sustained physical effort, it's logical to consider iron-deficiency anemia. And, what Tabron can do once the diagnosis is confirmed.

#### Each Tabron Filmseal® tablet represents:

rerrous fumarate (represents 100 mg of
elemental iron) 304.2 mg
Vitamin C (ascorbic acid) 500 mg
Vitamin B <sub>1</sub> (thiamine mononitrate) 6 mg
Vitamin B <sub>2</sub> (riboflavin) 6 mg
Vitamin B <sub>6</sub> (pyridoxine hydrochloride) 5 mg
Vitamin B <sub>12</sub> (cyanocobalamin), crystalline 25 mcg
Folic acid* 1 mg
Nicotinamide (niacinamide) 30 mg
Calcium pantothenate 10 mg
Vitamin E (dl-alpha tocopheryl acetate), (30 mg) 30 IUt
Dioctyl sodium sulfosuccinate 50 mg

\*CAUTION—Folic acid may obscure pernicious anemia; the peripheral blood picture may revert to normal while neurological manifestations remain progressive.

†III=International Units

CAUTION—Federal law prohibits dispensing without prescription

# TABRON® CORRECTS IRON-DEFICIENCY ANEMIA

PARKE-DAVIS

Div of Warner-Lambert Co

<sup>\*</sup>supplied as 304.2 mg of ferrous fumarate

#### American Journal of Obstetrics and Gynecology

Copyright © 1980 by The C. V. Mosby Company

Editors

John I. Brewer, Editor in Chief 710 North Fairbanks Court, Chicago, Illinois 60611

Frederick P. Zuspan, Editor

The Ohio State University, 410 W. 10th Ave., Columbus, Ohio 43210

#### Information for authors

Submission of contributions. Manuscripts should in general be sent to a particular Editor according to the following plan: If it is from the southeastern quadrant of the United States or from Canada, or if it has been presented before one of the official sponsoring societies, to Dr. Brewer; if from the northeastern quadrant (including Ohio), or if it is a Clinical Opinion or a Letter to the Editors, to Dr. Zuspan; if from the north central states, any of the United States west of the Mississippi, Hawaii, Alaska, or abroad, to Dr. Quilligan.

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following written statement, signed by one author: "The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C. V. Mosby Company in the event the work is published. The undersigned author warrants that the article is original, is not under consideration by another journal, and has not been previously published. I sign for and accept responsibility for releasing this material on behalf of any and all co-authors." Authors will be consulted, when possible, regarding republication of their material.

All articles published in this JOURNAL must be contributed to it exclusively. Articles previously published in another language are not acceptable.

It is assumed by the Editors that articles emanating from a particular institution are submitted with the approval of the requisite authority.

Articles dealing with human experimentation cannot be accepted unless the experiment was approved by the author's local Human Experimentation Committee.

Statements and opinions expressed in the articles and communications herein are those of the author(s) and not necessarily those of the Editor(s) or Publisher and the Editor(s) and Publisher disclaim any responsibility or liability for such material. Neither the Editor(s) nor the Publisher guarantee, warrant, or endorse any product or service advertised in this publication, nor do they guarantee any claim made by the manufacturer of such product or service.

Manuscripts. Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. The original and one copy of the manuscript are required. References should be placed at the end of the article. They should include name of author(s), article title, name of periodical, volume, page, and year. Name of periodical should conform to that shown in latest List of Journals Indexed in Index Medicus. For reference style see current issue of JOURNAL. Authors are encouraged to limit references to 16, except for Communications in Brief, limited to 2, Current Investigation and Clinical Opinion, limited to 6, and Current Developments, for which there is no limit. Illustrations accompanying manuscripts should be numbered, provided with suitable

E. J. Quilligan, Editor

University of California, Irvine, Medical Center, Department of Obstetrics and Gynecology, Building 16, 101 City Dr. S., Orange, California 92668

Albert B. Gerbie, Associate Editor
710 North Fairbanks Court, Chicago, Illinois 60611

legends, and marked lightly on the back with the author's name. Authors should indicate on the manuscript the approximate position of tables and text figures.

Tables should be typed on separate sheets of paper, not in the text, with one table to a page. They should be numbered in sequence and each must be referred to at an appropriate point in the text. Captions of the tables should be brief, yet indicate clearly the purpose or content of each table. Rows and columns in the table should precisely define the nature of the data in each. Abbreviations in tables should be used as little as possible and if abbreviations are used they should be explained in a footnote to the table.

An abstract of 50 to 150 words, to be published as an introduction, should accompany each manuscript and should be typed on a separate sheet of paper.

A footnote should be included which gives the name and complete mailing address of the person to whom reprint requests and correspondence should be sent.

A Guide to Writing for the American Journal of Obstetrics and Gynecology may be obtained from the Publisher on request.

Illustrations. A reasonable number of halftone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the Editors for color plates, elaborate tables, or extra illustrations. Original drawings or graphs should be drawn with black India ink. Typewritten or freehand lettering is not acceptable. All lettering must be done professionally. Do not send original art work, x-ray films, or ECG tracings. Glossy print photographs are preferred, for good black and white contrast is essential. Illustrations will be returned only if requested by the author.

Announcements. Announcements of meetings must be received by Dr. Brewer at least 2½ months prior to the time of the meeting. Such announcements should concern major meetings and other significant activities. Announcements of symposia or seminars for which fees are charged are not published in the scientific pages of the JOURNAL but may be submitted for paid advertisements, if desired.

Letters to the Editors. A brief Letter to the Editors commenting upon some article which has appeared in the JOURNAL will be considered for publication. The writer of the original article will have an opportunity to reply to unfavorable comments. A brief case presentation of special interest in the form of a Letter to the Editors will also be considered for publication. All such letters should be sent to Dr. Zuspan.

**Books.** Books received will be listed in the JOURNAL. They should be sent to Dr. Gerbie.

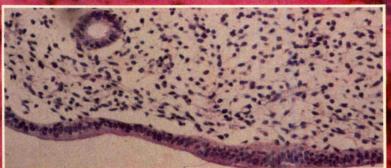
Reprints. Reprints of articles must be ordered from the Publishers, The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141, who will send their schedule of prices. Individual reprints of an article must be obtained through the author

# SPOT-RESISTANT ORAL CONTRACEPTION IS HERE!

It's LO/OVRAL 30. And here's how it holds spotting and breakthrough bleeding to a minimum: Hormone balance right from the start...and throughout the cycle. Hormone balance made possible with a very low dose oral contraceptive because of the supportive progestational activity of norgestrel, Wyeth's exclusive progestogen.

Regular withdrawal bleeding, too despite its low dose. In clinical trials amenorrhea—defined as absence of bleeding in the 7 pill-free days—was reported in only 2.1% of total cycles. And when defined as absence of bleeding for 60 days or more (as it often is), the incidence was only 0.2%.\*

And comfort for most patients\* thanks to the same balance that helps prevent spotting and breakthrough bleeding. In the clinical trials, most patients stayed free of common side effects such as nausea (0.6% of cycles), vomiting (0.1%), depression (0.5%) and acne (0.9%).



#### LO/OVRAL—1st cycle

Biopsy of intact endometrium in stable, progestogen suppressed state. Small, tubular gland in loose stroma without hemorrhage, fragmentation or debris characteristic of desquamating endometrium.

Even in the first cycle, the effective action of LO/OVRAL on the endometrium, such as you see here, provides the resistance against spotting and breakthrough bleeding you hope to achieve.

# HISTOLOGICALLY... AND CLINICALLY.

4.2% SPOTTING

Cycle 1—10.6%; Cycle 3—6.3%; Total Cycles—4.2%

2.9% BREAKTHROUGH BLEEDING

Cycle 1—8.8%; Cycle 3—3.3%; Total Cycles—2.9%

100%

A near-spotless record in clinical trials involving 22,489 cycles\*

\*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. Contraindications, Warnings, Precautions, Adverse Reactions, etc., in the accompanying In Brief should be carefully considered.

See full prescribing information.

# LOOVRA BOOK

each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol, Wyeth

...with a near-spotless record!

IN BRIEF:
Indications and Usage—LO/OVRAL® is indicated for the prevention
of pregnancy in women who elect to use oral contraceptives (OC's)
as a method of contraception.

any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders.

Cerebral-vascular or coronary-artery disease. Known or suspected carcinoma of the breast

4. Known or suspected carcinoma of the breast.
5. Known or suspected estrogen-dependent neoplasia.
6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5). 8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products.

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be

years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information statistics be these risks. relating to these risks

Thromboembolic Disorders and Other Vascular Problems-An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause. diseases without evident cause

diseases without evident cause. CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking) is considered a major predisposing condition to MI) are

regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S. ESTIMATE oF EXCESS MORTALITY FROM CIRCULATORY

DISEASES—A large prospective study carried out in the U.S. ESTIMATE oF EXCESS MORTALITY FROM CIRCULATORY

DISEASES—A large prospective study carried out in the U.S. estimated the mortality rate per 100, 000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years are available from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophelbitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolic complications has been reported in OC users.

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

2. Ocular Lesions—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papifiedema; or refinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

papineuenia, or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. Carcinoma—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary podules, basics.

and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the "irst 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 cm OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroup of OC users with documental basing houses. endometrium in women under 40 an OC's. Of cases found in of OC users with documented benign breast disease. Reduced occurrence of benign breast turnors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is nevertheless, essential. In all cases of undiagnosed persistent or re-current abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular carrief they elect to use OC's.

if they elect to use OC's.

4. Hepatic Tumors—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk heigh much praster after 4 or more version.

inenformage. Inis has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OCs, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live pirths. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy. 6. Gallbladder Disease—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was paparent between 6 and ner studies, increased risk was apparent between 6 and

12 months' use 12 months use.

7. Carbohydrate and Lipid Metabolic Effects—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and to:al phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined.

be defined.

8. Elevated Blood Pressure—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of Lse, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who prevously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. Headache—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. Bleeding Irregulanties—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing 8. Elevated Blood Pressure—Increase in blood pressure has

vaginal bleeding, nonfunctional causes should be borne in mind In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities. irregularities.

11. Ectopic Pregnancy—Ectopic as well as intrauterine

Irregularities.

11. Ectopic Pregnancy—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. Breast-feeding—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome

retention, such as convulsive disorders, migrane syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

relevant specimens are submitted.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI). T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling. Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

tetracycline.

Carcinogenesis — See Warnings on carcinogenic potential of OC's
Pregnancy — Category X. See Contraindications, Warnings.

Mursing Mothers — See Warnings.

Adverse Reactions — An increased risk of these serious adverse

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings); thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, galibladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g. retinal thrombosis and optic neuritis. The following adverse reactions have been reported in patients on OC's and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; temporary infertility after which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical servicing possible diministrics in cervical servicins processible diministrics in cervical servicins processible diministrics in and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution is lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to

rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses. The tollowing adverse reactions have been reported in users of OCs, and the association has been neither confirmed nor refuted; premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young

following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.



#### American Journal of Obstetrics and Gynecology

volume 138 number 3

Остовек-1, 1980

#### **OBSTETRICS**

### Outcome of pregnancy in sickle cell anemia and sickle cell-hemoglobin C disease

An analysis of 181 pregnancies in 98 patients, and a review of the literature

PAUL F. MILNER, M.D. BENNIE R. JONES, L.P.N. JOHANNA DÖBLER, B.Sc. Augusta, Georgia

The outcome of pregnancy has been analyzed in 72 women with sickle cell anemia (SS) and 26 women with sickle cell-hemoglobin C disease (SC), part of an unselected population of 148 women over 18 years of age with these hemoglobinopathies, who have been followed at a sickle cell disease clinic for 8 years. In SS women, 22% of first pregnancies were aborted spontaneously, and the overall early fetal loss was 19.2%. A similar figure was calculated from the literature since 1956. In SC women, 12% of first pregnancies were lost, but the overall early fetal loss was only 8.9%. The perinatal mortality, under quite variable conditions of prenatal care and delivery, was 10.2% in SS women and 2% in SC women. There were no stilloi this or midterm deaths in utero among SC women, but these accounted for most of the perinalal mortality in SS women, particularly in first and second pregnancies. There was one neonatal death in each group, but eight third pregnancies in SS women were completed without perinatal mortality. A remarkable finding among the SC women was the number of successful pregnancies, ten in one woman, and many of the pregnancies were completed without the supervision of a physician. Our findings were compared with those in the literature, and the conclusion that we drew is that termination of pregnancy and sterilization of young women are not generally indicated solely on the basis of these hemoglobinopathies. (Am. J. OBSTET. GYNECOL. 138:239, 1980.)

MANY PHYSICIANS and obstetricians hold the view that women with sickle cell anemia (SS) and sickle

From the Departments of Pathology, Medicine, and Cell and Molecular Biology, and the Sickle Cell Center, Medical College of Georgia.

Supported by United States Public Health Service Gram HLB-15158.

cell-hemoglobin C disease (SC) should be advised not to have children, and some would even advise termina-

Received for publication May 13, 1980.

Accepted June 10, 1980.

Reprint requests: Dr. Paul F. Milner, Sickle Cell Center, Médical College of Georgia, Augusta, Georgia 30901.

Table I. Outcome of pregnancy in SS women

Pregnancy	No.	Induced abortions	Spontaneous abortions	Death in utero	Viable fetuses	Still- births	Liye births	Neonatal deaths	Perinatal deaths (%)	Infant deaths	Children alive now
First	72	9	13	1	50 (1 twin)	5	45	1	13.3	2 (cot deaths)	42
Second	36	4	. 3	1	29 (1 twin)	3	26	0	11.5	4	22
Third	12	1	3	0	8	0 ·	8	0	-	0 .	8
Fourth	3	0	2	0	1	0	1	0		0	1
Totals	123	14	21	2	88 (2 twin)	8 .	80	1	10.2	6	73

Table II. Outcome of pregnancy in SC women

Pregnancy	No.	. Induced abortions	Spontaneous abortions	Viable Jetuses	Still- births	Live births	Neonatal deaths	Surviving children
First	25	0	3	22	0	22	1	21
Second	14	2	2	10	0	10	0	10
Third	8	0	0 .	8	0	8	0	√ 8
Fourth	5	0	0	5	0	5	0	5
Fifth	5	0	0	5	0	5	0	5
Sixth	1	0	0	1	0	. 1	. 0	1
Totals	58	2	5	51	0	51	1	50

tion of pregnancy and permanent sterilization in all cases. When this advice is not acceptable, exchange transfusion early in pregnancy, or at least throughout the last trimester, is considered by some obstetricians to be mandatory, although the need for this in many cases has recently been questioned. 3, 4

The present report is concerned with the obstetric experiences of 72 women with SS and 26 with SC disease, part of a group of 148 women over 18 years of age with sickle cell diseases being followed at the Sickle Cell Center of the Medical College of Georgia, in Augusta. Their experience spans 40 years and reflects the obstetric practices in various hospitals and obstetric departments, mostly in rural areas, rather than the results in one department or institution. In several instances, babies were born at home without medical supervision. The incidence of spontaneous abortions, intrauterine deaths, stillbirths, and neonatal deaths is compared with the incidence of these complications reported in the literature. The incidence of termination and sterilization, and the indications for these measures, are also discussed.

#### Patients and methods

Hematologic diagnoses were made by hemoglobin (Hb) electrophoresis in alkaline and acid media, Hb S solubility tests, and measurement of Hb A<sub>2</sub> by column chromatography. Hemograms were obtained by Coulter counter, and blood smears were examined for typical red cell morphologic features. Women who were

considered to have Hb S/ $\beta$ -thalassemia or Hb S/hereditary persistence of fetal hemoglobin have been excluded from this discussion. Some of the homozygous SS women probably have genes for  $\alpha$ -thalassemia, sa evidenced by low mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) values and a low proportion of Hb S in their parents and siblings. Most of the offspring of the patients discussed have been tested and found to have Hb S trait or, in some of the offspring of the SC women, Hb C trait.

Direct inquiry was made of each woman with regard to her obstetric history, age at menarche, age at each pregnancy, outcome of each pregnancy, and survival of her offspring. Whenever possible, hospital records were scrutinized to check the data, and information in regard to blood transfusions and other treatments was obtained. Only one of the patients has died, an SS gravida 4, para 3, abortion 1, who died in renal failure at the age of 48. All the other patients have been seen within the last 2 years.

#### Results

The outcome of 123 pregnancies in 72 SS women is shown in Table I, and that of 58 pregnancies in 25 SC women is shown in Table II. One other SC woman, now 61 years old, had 15 remembered pregnancies, five of which were lost as miscarriages and ten were carried to term. All ten infants were delivered at home by midwives, and for only one was a doctor called in to assist.

Spontaneous abortions. Twenty-two percent of first pregnancies in SS women were lost, but only 9.4% of second pregnancies. There were too few third and fourth pregnancies in SS women to make a comparison, but 36% of these were aborted. This makes a total of 21 of 109 pregnancies (allowing for 14 which were terminated) that ended in spontaneous abortion, an early fetal loss of 19.2%. Only three of 25 first pregnancies in SC women were aborted (12%), whereas two of 12 second pregnancies were lost, but none in 19 further pregnancies, so that the overall early fetal loss was 8.9%.

Perinatal mortality. There were no stillbirths or midterm deaths in utero among SC women, and only one neonatal death occurred, in a primigravida, to give a perinatal mortality of 2%. By contrast, the perinatal mortality associated with SS disease was 10.2% (Table I), all in first and second pregnancies. Among 80 live births, there was only one neonatal death. Of 36 women who have remained primigravidas, 25 had a viable child (one had twins, one of whom was born dead), seven had termination of pregnancy, three aborted spontaneously, and one suffered the death of her infant in utero at midterm. Of 36 women who had a second pregnancy, nine had lost their first child by spontaneous abortion, and two of these aborted again; two had had a termination of their first pregnancy and had the second terminated, also; one desired termination for the second pregnancy since she had a live child; and one, age 19, was advised to have a termination although she had had no complications during the first pregnancy. Among the 36 second pregnancies, there were 26 live births, one of which was a twin. Eight third pregnancies carried to term resulted in eight live births with no perinatal mortality. Of the three SS women who had a fourth pregnancy, one has had spontaneous abortion of all four, one had a spontaneous abortion of the fourth but has three live children. and the third woman's fourth child survived. In summary, for this group of 72 women, there were 88 viable fetuses, 79 of whom survived the perinatal period (89.8%).

Sterilization and termination of pregnancy. The gravidity, parity, and mean age at sterilization of SS women are shown in Table III. Four of 13 sterilizations in primigravidas were performed in association with termination of pregnancy, whereas three other women had terminations of pregnancy without sterilization. Four sterilizations followed delivery of a live fetus. Thirty-six percent of primigravidas have been sterilized. Of 36 SS women who became pregnant a second time, 14 were sterilized (39%), but only one of these tubal ligations followed a termination of pregnancy

'Table III. Sterilization of SS women

Gravida	Para	Patients	No. sterilized	% sterilized	Age (yr)
	0	11	4*	36.4	20-25
I	1	25†	9 .	36.0	19-24
Total		36‡	13 .	36.1	19-25
2	0	3‡	2	66.6	23,25
2	1	6	3	50.0	19-25
2	2.	15‡	8	60.0	19-34
Total		24†	13	<b>54.1</b>	19-34
3 .	0	0	0	-	_
3	1	3	1	33.3	19
3	2	4	3	75.0	20-31
3	. 3	2	2	100.0	23,26
Total		9	6	66.6	19-31
4	0	1	0		-
- 4	1	0.	0	-	_
. 4	2	0	0		_
4	3	1	- 0	-	_
4	4	1	1	100.0	27
Total	,	3	1	33.3	27

<sup>\*</sup>Two had a hysterectomy to remove the fetus.

Ten were carried out after a live birth, and two after stillbirths. Six of nine women who were gravida 3 have been sterilized, but only one of the three who were gravida 4.

Four SC women have been sterilized. One was a partially disabled 14-year-old who had been delivered of a live baby. Two were 16 and 17 years old at the time of their second pregnancies, and one requested tubal ligation at 19 years of age after a third pregnancy and delivery.

#### Case report

From the case notes: "This is a 16-year-old black female, gravida 2, para 1. She has SC-disease and is 22 weeks pregnant at the present time. She was seen in OB Clinic requesting abortion. Upon review of the current figures on maternal and perinatal mortality and morbidity in mothers with SC disease, the patient was counseled regarding these figures and she made the decision to have an abortion and also permanent sterilization. She has one living child and claims to desire no more children."

After minilaparotomy and bilateral tubal ligation, the pregnancy was terminated by amniocentesis and prostaglandin infusion. It seemed clear that at that time this woman desired no more children, but 4 years later, she returned and wanted to have the tubal ligation repaired because she was then getting married.

#### Comment

Eisenstein and associates<sup>6</sup> reviewed the literature prior to 1956, and found reports on 129 women with

<sup>†</sup>Two subsequently had a hysterectomy.

<sup>. ‡</sup>One subsequently had a hysterectomy.

Table IV. Pregnancy outcome in 203 SS patients reported in the literature since 1956

Author	No. of patients	Pregnancies	Spontaneous abortions	Viable fetuses	Still- births	Live births	Neonatal deaths	Perinatal mortality (%)	Maternal deaths
Curtis, 15 1959	9	21	4	17	6	11	0	35.3	0
Johns Hopkins									
Abrams and Schwartz, 16 1959 Philadelphia	6	30*	8*	22	1	. 21	0	4.5	0
Anderson et al., <sup>17</sup> 1960 Kingston, Jamaica	9	17	1	16	2	14	0	12.5	0
Lansford and Stander, 10 1960 Indianapolis, Indiana	3	4	0	4	1	3	0	25.0	0
Ricks, <sup>18</sup> 1961 Chicago, Illinois	9	25	7	18	2	16	2	22.2	2†
McCurdy, <sup>19</sup> 1964 Washington, D. C.	19	52	Total fetal loss, 18	?	?	. 34	?	?	1
Hendrickse et al.,7 1972	38	74 (3 twin)	11	66	4	62	8	18.2	7
Ibadan, Nigeria Freeman and Ruth, 11 1969	18	41	11	33	4	29	1	15.1	0
Atlanta, Georgia Perkins, 20 1971	23	(3 twin) 50	10	41	5	36	1	14.6	0
Sloane Hospital, New York Fort et al., 1971	35 ·	(2 twin) 97	15	82	18	64	14	39.0	6
Memphis, Tennessee Fiakpui and Moran, <sup>21</sup> 1973 Chicago, Illinois	13	14	0	14	2	12	0	14.2	1‡
Horger, <sup>22</sup> 1972 Charleston, South Carolina	40	45§ (2 twin)	7	40	4	36	0	10.0	1‡
Pritchard et al.,8 1973 Dallas, Texas	34	50	16	36	5	31	4	25.0	0
Total	256	468¶	90 (19.2%)	389	54	325¶	30	21.6	18

<sup>\*</sup>Only 10 live births observed by the author.

sickle cell disease, but the distinction between SS, SC, and  $S/\beta$ -thalassemia was not always made. They added nine cases of their own. Among these 138 patients, 30 of whom died, there were 286 pregnancies; the maternal mortality was 21.7% or 10.5 deaths per hundred pregnancies. The spontaneous abortion rate was 19.3%, the perinatal mortality was 22.5%, and the total fetal wastage was 41.9%. Despite these findings, Eisenstein and associates6 concluded that sickle cell disease had little or no effect on labor, that its greatest effect was on the fetus, and that the effect of pregnancy on the sickle cell disease was not clearly established, except for an increased incidence of maternal infections. They considered that sickle cell anemia was not an indication for therapeutic abortion, but that sterilization should be considered in women who already had children.

The literature since Eisenstein and associates is summarized in Table IV. For 15 years after Eisenstein and associates' report, maternal death in SS women was not a feature, except in a report from West Africa, in 1966,<sup>7</sup> where, under somewhat primitive conditions, there were 9.4 maternal deaths per hundred pregnan-

cies. Then in 1971, in a report from Memphis, Tennessee, Fort and associates1 made a retrospective survey of 97 pregnancies in 35 SS women and reported six fatalities (6.2 per hundred pregnancies) and indicated that, in the more typical patients, the perinatal mortalty was 51% to 55%. They estimated the maternal mortality in such cases to be 10% to 14%, and advised, therefore, that all SS women should be counseled to accept primary sterilization and abortion if conception occurred, with sterilization of those who had completed pregnancies. Scrutiny of Table IV, however, reveals that, if the maternal deaths from Memphis and those from Africa, where prenatal care was largely lacking, are omitted, there were only five deaths in 385 pregnancies, or 1.3 per 100, and four of these were associated with pneumonia or severe infections. In a recent review on the management of sickle cell disease in pregnancy, Charache and associates4 arrived at a similar figure, 1.6%, for SS maternal deaths in six large obstetric units around the nation over the past 20 years.

The last full review of the course and outcome of pregnancy in SS disease, published in 1973,8 gave. a

<sup>†</sup>One had staphylococcal infection and pyelonephritis, and the other had fulminating bronchopneumonia and a lung abscess. ‡Pneumonia.

<sup>§</sup>Of 36 previous gestations not observed by the author, there were 20 surviving children.

<sup>¶</sup>The 52 pregnancies and 34 live births reported by McCurdy 19 are excluded from the total.

Table V. Pregnancy outcome in 201 SC patients reported in the literature since 1956

Author	No. of patients	Pregnancies	Spontanzous abortions	Viable fetuses	Still- births	Live births	Neonatal deaths	Perinatal mortality (%)	Maternal deaths
Curtis, 15 1959	16	43	7	. 36	8	28	0	22.2	4*
Johns Hopkins	•								
Abrams and Schwartz, 16 1959	3	15	0	15	0	15	0	0	0
Philadelphia									
Sackner et al., <sup>23</sup> 1959	4	19	. 0	19	0	19	0	0	0
Philadelphia									
Anderson et al., <sup>17</sup> 1960	7	17	2	15	0	15	0	0	0
Kingston, Jamaica	_		_	_	_		_		_
Lansford and Stander, 10 1960	2	11	3	8	1	7	0	12.5	0
Indianapolis, Indiana						**			
River et al., 12 1961	25	87	17	72	3	69	0	4.1	0
Cook County, Chicago	• •	(2 twin)	2	*0		*^	•		~
McCurdy, 19 1964	14	59	9	50	0	50	0	0	0
Washington, D. C.		0.7		0.0		=0		1.0	
Laros, <sup>24</sup> 1967	14	67	7†	60	1	59	0	1.6	1‡
Philadelphia Philadelphia	00	0.1			0	40		0.0	
Freeman and Ruth, 11 1969	23	61	11	51	2	49	3	9.8	0
Atlanta, Georgia		(1 twin)	00	9.77		0.5	•	0.1	C.
Perkins, <sup>20</sup> 1971	17	59	22	37	2	35	1	8.1	0
Sloane Hospital, New York	15	35	8	26	5	21	0	26.9	3
Fort et al., 1971	15	33	8	20	5	21	2	20.9	0
Memphis, Tennessee	9	17	0	16	5	11	0	31.2	9.0
Horger, <sup>22</sup> 1972 Charleston, South Carolina	9	17 .	2	10	3	11	U	31.2	3§
Pritchard et al.,8 1973	43	78	5	75	5	70	2	9.3	2¶
Dallas, Texas	753	(2 twin)	υ,	10	5	70	2	9.0	41
•		•							
Total	201	581	85	493	32	461	8	8.1	13

Abortion rate, 14.6%. Maternal mortality, 2.2 per 100 pregnancies.

cautious, but more optimistic, prognosis for pregnancies if they were managed carefully. Since that time, more frequent and careful use of blood transfusion, more vigorous treatment of infections, and better assessment of the fetus have almost eliminated maternal deaths and considerably lowered perinatal mortality.<sup>4, 5</sup> However, there is still room for improvement in the delivery of prenatal care, especially in rural areas, and a need for a way to predict complications in individual patients.

The literature on the outcome of pregnancy in SC disease is summarized in Table V. Lansford and Stander, <sup>10</sup> in 1960, concluded that, "Therapeutic abortior does not seem indicated in patients with this disease Sterilization in these patients must be considered on an individual bases." Freeman and Ruth, <sup>11</sup> in 1969, although they found no maternal mortality, remarked that, "There are too many well-documented fatalities associated with Hb SC disease for anyone to feel complacent about the disease. For these patients pregnancy

represent an unnecessary risk." They did, however, concede that the variability of the disease made difficult any generalizations about prognosis. River and associates<sup>12</sup> found no maternal deaths despite 87 pregnancies in 25 SC women. Of the 13 deaths listed in Table V (2.2 per 100 pregnancies), most were associated with pneumonia or pulmonary infarction. The perinatal mortality in this literature was 8.1%.

From the data on the outcome of pregnancy in women with SC disease presented in this report, it seems that the advice of Lansford and Stander has largely been followed, although several of our patients had their babies without much medical counseling, and, indeed, many of them were not known to have SC disease at the time of their pregnancies and deliveries. The literature on SC disease may have a bias in this respect since SC disease is frequently not detected in routine hospital admissions, outside of teaching units, and the deaths and complications are more likely to be reported than the unknown or benign cases. Some

<sup>\*</sup>Two with widespread infarction of bone, pulmonary empolism, and fat embolism. One with pain crises—no autopsy performed. One postpartum hemorrhage.

<sup>†</sup>Includes one maternal death and one ectopic pregnancy.

<sup>‡</sup>Bilateral lower lobe pneumonia at 13 weeks' gestation.

<sup>§</sup>One puerperal sepsis; one ruptured uterus, undiagnosed during life; one pulmonary infarction at 37 weeks.

<sup>¶</sup>One seen for the first time in labor with severe preeclampsia. One seen near term for the first time with pulmonary infarct.

physicians may need to revise their impression, gleaned from the literature, particularly when considering indications for primary sterilization and termination of pregnancies.

The variability in severity within the SS genotype<sup>13</sup> makes prognosis difficult, and at the present time there is no certain way to predict the course or outcome of the pregnancy in any given case.14 Women need to be aware of the high rate of spontaneous abortion and perinatal mortality, but these facts, of themselves, do not necessarily indicate sterilization and termination of existing pregnancies. Fort and associates gave two further reasons for counseling: because of her illness, the mother cannot care for the child; and the child may also inherit the homozygous disease. The sociology of black families frequently allows for the grandmother to raise the children, and children are frequently desired for support in later life. Most SC women have only a mild anemia and are infrequently ill. The intense desire of some SS women to have at least one child, despite their illness, cannot logically be denied on eugenic grounds, provided that hemoglobin testing of the fathers is promoted and counseling is made available. Much money is presently being spent on testing, educating and counseling carriers of the sickle cell trait, and it is at this level that awareness of the genetic significance of the disease should be promoted. After all, the disease is expressed clinically as a recessive gene, so that all the children of an SS mother by an AA father will be clinically normal.

The general obstetrician and family practitioner need to be aware of the better prognosis for these patients and to treat each case individually. Nevertheless, those patients who wish to become pregnant or proceed with a pregnancy should be advised to obtain their prenatal care and delivery at a high-risk pregnancy unit. The right time to administer blood transfusions, if indicated, can then be decided, and, by careful blood group typing, the development of blood group antibodies can be avoided. At present, the haphazard, and largely unnecessary, use of blood transfusions to treat these patients during attacks of pain makes it increasingly more difficult to find compatible blood when a real indication, such as pregnancy, arises.<sup>9</sup>

In our experience, the spontaneous abortion rate in SS women was 19.2%. It is interesting that Eisenstein and associates6 found a 19.3% rate, and the accumulated literature since their review shows a 19.2% rate. Such agreement in three groups which totaled over 400 patients suggests that this is one figure on which we can rely. Blood transfusions are very rarely given during the first trimester, the period in which most of these abortions occur, because the usual indications of increasing anemia or repeated pain crises do not usually arise at that time. Different therapeutic approaches to the problems of pregnant women with sickle cell anemia have, therefore, not affected the early fetal loss. Any future plans for improving the course of pregnancy in these patients should take this early loss into account.

#### REFERENCES

- Fort, A. T., Morrison, J. C., Berreras, L., Diggs, L. W., and Fish, S. A.: Counseling the patient with sickle cell disease about reproduction: Pregnancy outcome does not justify the maternal risk, Am. J. OBSTET. GYNECOL. 111:324, 1971.
- Morrison, J. C., and Wiser, W. L.: The use of prophylactic partial exchange transfusion in pregnancies associated with sickle cell hemoglobinopathies, Obstet. Gynecol. 48:516, 1976.
- 3. Editorial: Transfusion therapy in pregnant sickle cell disease patients, Am. J. Obstet. Gynecol. 134:851, 1979.
- Charache, S., Scott, J., Niebyl, J., and Bonds, D.: Management of sickle cell disease in pregnant patients, Obstet. Gynecol. 55:407, 1980.
- Felice, A. E., Webber, B., Miller, A., et al.: The association of sickle cell anemia with heterozygous and homozygous α-thalassemia-2, Am. J. Hematol. 63:91, 1979.
- Eisenstein, M. I., Posner, A. C., and Friedman, S.: Sickle cell anemia in pregnancy, Am. J. Obstet. Gynecol. 72:622, 1956.
- Hendrickse, J. P. de V., Harrison, K. A., Watson-Williams, E. J., Luzzatto, L., and Ajabor, L. N.: Pregnancy in homozygous sickle cell anemia, J. Obstet. Gynecol. Br. Commonw. 79:396, 1972.

- 8. Pritchard, J. A., Scott, D. E., Whalley, P. J., Cunningham, F. G., and Mason, R. A.: The effects of maternal sickle cell hemoglobinopathies and sickle cell trait on reproductive performance, Am. J. Obstet. Gynecol. 117:662, 1973.
- Cunningham, F. G., Pritchard, J. A., Mason, R., and Chase, G.: Prophylactic transfusions of normal red blood cells during pregnancies complicated by sickle cell hemoglobinopathies, Am. J. Obstet. Gynecol. 135:994, 1979.
- Lansford, K. G., and Stander, R. W.: Sickle cell anemia in pregnancy, Obstet. Gynecol. 16:194, 1960.
- 11. Freeman, M. G., and Ruth, G. J.: SS disease, SC disease and CC disease—Obstetric considerations and treatment, Clin. Obstet. Gynecol. 12:134, 1969.
- 12. River, G. L., Robbins, A. B., and Schwartz, S. O.: S-C hemoglobin: A clinical study, Blood 18:385, 1961.
- Perrine, R. P., and John, P.: Pregnancy in sickle-cell anemia in a Caucasian group, Am. J. Obstet. Gynecol. 118:29, 1974.
- 14. Powars, D. R., Schroeder, W. A., Weiss, J. N., et al.: Lack of influence of fetal hemoglobin level or erythrocyte indices on the severity of sickle cell anemia, J. Clin. Invest. 65:732, 1980.
- 15. Curtis, E. M.: Pregnancy in sickle cell anemia, sickle

- cell-hemoglobin C disease and variants thereof, Am. J. Obstet. Gynecol. 77:1312, 1959.
- Abrams, J., and Schwartz, I. R.: The sickle cell diseases in pregnancy, Am. J. OBSTET. GYNECOL. 77:1324, 1959.
- Anderson, M., Went, L. N., MacIver, J. E., and Dixon, H. G.: Sickle-cell disease in pregnancy, Lancet 2:513, 1960.
- 18. Ricks, P.: Sickle cell anemia and pregnancy; Obstet. Gynecol. 17:513, 1961.
- McCurdy, P. R.: Abnormal hemoglobins and pregnancy, Am. J. Obster. Gynecol. 90:891, 1964.
- 20. Perkins, R. P.: Inherited disorders of hemoglobin syn-

- thesis and pregnancy, Am. J. Obstet. Gynecol. 111:120, 1971
- 21. Fiakpui, E. Z., and Moran, E. M.: Pregnancy in the sickle hemoglobinopathies, J. Reprod. Med. 11:28, 1973.
- 22. Horger, E. O.: Sickle cell and sickle cell-hemoglobin C disease during pregnancy, Obstet. Gynecol. 39:873, 1972.
- 23. Sackner, M. A., Dex, W. J., and Kaplan, A. I.: Sickle cell-hemoglobin C disease and pregnancy, including a case of ostcomyelitis, Am. J. Obstet. Gynecol. 77:1328, 1959.
- Laros, R. K.: Sickle cell disease and pregnancy, Pa. Med. 70:73, 1967.

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following written statement, signed by one author: "The undersigned author transfers all copyright ownership of the manuscript (title of article) to The G. V. Mosby Company in the event the work is published. The undersigned author warrants that the article is original, is not under consideration by another journal, and has not been previously published. I sign for and accept responsibility for releasing this material on behalf of any and all co-authors." Authors will be consulted, when possible, regarding republication of their material.

#### Analysis of heart rate and beat-to-beat variability: Interval difference index

HERMAN P. VAN GEIJN, M.D., PH.D.
HENK W. JONGSMA, PH.D.

JELTE DE HAAN, M.D., PH.D.\*

TOM K. A. B. ESKES, M.D., PH.D.

Nijmegen, The Netherlands

The relationship between the RR interval length (RR) and the RR interval-to-interval differences (RR differences) was investigated. Data on heart rate were obtained from 11 newborn iniants in well-defined behavioral states undergoing polygraphy. It was found that the RR differences were strongly dependent on the RR interval length in all behavioral states. The relationship between the RR differences (y) and the interval length (RR) could be described by the equation  $y = \alpha (RR-320)^{1.5}$  for the interval length in the investigated range from 375 to 605 msec. On the basis of this relationship the interval difference index (ID index) was constructed for the quantification of beat-to-beat heart rate variability. The ID index showed good independence from the long-term irregularity index (LTI index). Other statistical parameters proposed for the quantification of beat-to-beat heart rate variability are discussed and compared with the ID index. (AM. J. OBSTET. GYNECOL. 138:246, 1980.)

THE HEART RATE of the healthy human being varies continuously. Heart rate variability is present at all ages from fetus to elderly. Variations in heart rate represent the moment-to-moment integration of the many mechanisms in and outside the central nervous system which regulate the heart rate. Conditions that cause a marked reduction in heart rate variability are, for example, the absence of regulating centers in the central nervous system, sedative drugs, and stress. 3

One way to analyze heart rate variability is to apply statistical parameters. Quantitative indices condense the large amount of information that results from continuous recordings of heart rate. The indices in use are generally based on the discrimination of at least two

From the Department of Obstetrics and Gynecology, Catholic University.

This research was supported by Grant 06273, Catholic University.

Received for publication March 15, 1980. Accepted April 30, 1980.

Reprint requests: Herman P. van Geijn, M.D., Ph.D., Department of Obstetrics and Gynecology, Free University, de Boelelaan 1117, 1031 HV, Amsterdam, The Netherlands.

\*Present address: Department of Obstetrics and Gynecology, State University of Limburg, St. Annadal Ziekenhuis, Maastricht, The Netherlands. types of heart rate variability: long-term and short-term variability.<sup>4–8</sup>

Short-term or beat-to-beat heart rate variability is actually measured by the differences between consecutive RR intervals.4-12 Most short-term variability indices can be formulated by a function which contains the RR differences multiplied by a factor that depends on the RR interval length.<sup>4, 5, 8, 11, 12</sup> In the human fetus, <sup>13</sup> newborn,14 and adult,15 the interval-to-interval differences decrease when the interval length decreases, and vice versa. Although most short-term variability indices contain a factor in which the RR interval length is included, this factor has not been derived from experimental analysis, but is an ad hoc choice. The dependence of the existing short-term variability indices<sup>4-12</sup> on the instantaneous heart rate hampers the study of circumstances which influence beat-to-beat variability when the baseline heart rate changes simultaneously.

The current study was an analysis of the relationship between RR interval differences and RR interval length. For this analysis, the subject of study had to be in a stationary situation. Influences that might have disturbed the relationship between interval differences and interval length had to be kept as small or constant as possible. For this purpose, heart rate data were obtained from newborn infants in well-defined behavioral states. Recordings of heart rate were made at fixed times of the day, under strictly standardized conditions. The relationship found between interval length and interval differences was used to define an index applicable for the quantitation of fetal and neonatal beat-to-beat variability.

#### Subjects and methods

Eleven healthy newborn infants (born spontaneously by the vaginal route; seven females, four males; Apgar scores 8 to 10; gestational ages of 39 to 42 weeks; birth weights of 2,700 to 4,070 grams (tenth to ninetieth percentiles): normal findings on neurological examination) underwent polygraphy during approximately 6 hours on days 4 to 6 after birth. From each polygraphic recording, epochs were selected with representative behavioral states. An epoch is the time during which the infant was in a certain behavioral state. A detailed description of the polygraphic techniques and the criteria applied for the assessment of the behavioral states were presented previously by Prechtl and associates. 16 The selected behavioral state epochs comprised 22 state 1 (quiet sleep) epochs, mean duration  $21 \pm 5$ minutes; 22 state 2 (active sleep) epochs, mean duration  $36 \pm 16$  minutes; and 14 state 3, 4, or 5 (drowsy, active, or crying state, respectively) epochs, mean duration  $17 \pm 11$  minutes. The number of awake states had to be limited because 75% to 90% of the time the newborn infant is asleep. Also during the awake states the electrocardiographic (ECG) signals were frequently disturbed by movement artifacts and did not lend themselves to optimal analysis.

The ECG signals obtained during the selected epochs were used for analysis of heart rate. The electrocardiogram was recorded on paper and magnetic tape (Bell and Howell, model VR 3700 E instrumentation recorder). After amplification, the analogue ECG signal was passed through a band-pass filter (15 to 60 Hz) and was led to a level detector. The RR interval length was digitized in time units of 0.8 msec. PDP-11 computers were used for further analysis. The analyzed heart rate data comprised the separate epochs of the individual infants and three collections consisting of the state 1 (A), the state 2 (B), and the combined states 3, 4, and 5 (C) epochs of all 11 newborn infants.

In order to compare the variability versus RR interval length relationship of the fetal heart rate with the neonatal data, a fetal electrocardiogram (FECG) tape was selected at random from among a group of such recordings obtained previously from healthy fetuses during early labor. These FECG recordings had been made with the use of a spiral fetal scalp electrode.

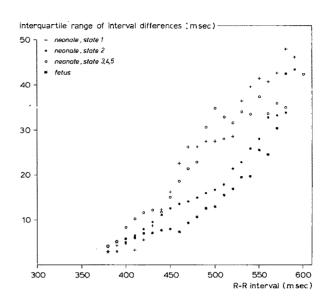


Fig. 1. The relationship between the RR interval length and the interquartile range of the interval differences in the newborn infants for the various behavioral states and in a healthy fetus at the beginning of labor.

Corometrics 111 fetal monitor, and Hewlett-Packard model 3960 A instrumentation recorder. Further processing of the FECG signal was carried out as described for the neonatal ECG records.

#### Analysis of RR interval-to-interval differences

The linkage of the heart rate data of all newborn infants according to the behavioral state made it possible to compare the interval differences over a wide range of interval lengths. The behavioral state epochs of the individual newborn infants were too short for this purpose and did not show enough variation of heart rate. The results of the analysis of the relationship between interval differences and interval length are presented in Fig. I. The mean length of two successive intervals (t<sub>i</sub>) is plotted on the horizontal axis. The interquartile range of the corresponding intervalto-interval differences (y<sub>i</sub>) is plotted in the vertical direction for each behavioral state, A, B, and C. The interquartile range of the RR interval differences was found to decrease, with a shortening of the RR interval length in all neonatal behavioral states and in fetal recordings. The analysis of the relationship between the interval length (t<sub>i</sub>) and the interquartile range of the interval-to-interval differences (y<sub>i</sub>) is described in detail in Appendix I. The relationship between the two variables could be written in the form,  $y_i = \alpha(t_i - t_0)^n$ . The parameters a, to, and n in this formula have been obtained by least-squares fit of the data in each behavioral state. Only the data in the range from 375 to 605 msec

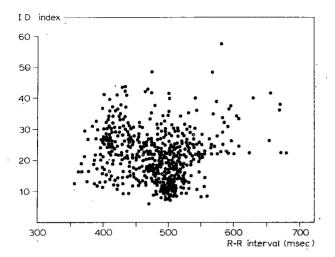


Fig. 2. The relationship between the median RR interval length and the interval difference index (ID index) in behavioral state 2 for a group of neonates.

were used. Outside this range, the number of observations was too small. The values of to and n obtained at an optimal fit varied only slightly for the various neonatal behavioral states and for heart rate data of healthy fetuses recorded at the beginning of labor. The values of  $t_0 = 320$  msec and n = 1.5 have been chosen as a compromise for all heart rate data. The symbol  $\alpha$ represents the amount of beat-to-beat variability. The value of  $\alpha$  will change when conditions that influence beat-to-beat variability change in an individual. The formula  $y_i = \alpha(t_i - 320)^{1.5}$  indicates that, for example, at 380 msec (158 beats/min) the beat-to-beat variability is ten times smaller than at 600 msec (100 beats/min), thus confirming the positive correlation between interval differences and interval length described earlier. 13-15 Below 380 msec the beat-to-beat variability might be reduced even more. However, not enough heart rate data were available in the range below 375 msec. Secondly, a higher precision in detecting interval length than that applied in the present study is needed for very small interval differences. The precision in the present study is primarily determined by the computer clock resolution of 0.8 msec.

#### Interval difference index (ID index)

The previous section described how the interquartile range of the interval-to-interval differences depends on the actual interval length. This relationship was applied in the interval difference index (ID index) constructed for the quantitation of beat-to-beat heart rate variability. The ID index quantifies the interval-to-interval differences over a period of 30 seconds and simultaneously takes into account the RR interval length present at any moment during these 30 seconds.

**Table I.** Correlation coefficients (r) for the median interval length (RR) and the ID index with respect to the STI index

	n	r(RR, ID index)	r(RR, STI index)
A (state 1)	745	0.13	0.73
B (state 2)	647*	-0.021	0.71
C (states 3, 4, and 5)	329	-0.034	0.72
D (fetus)	326	0.026	0.67

n = Number of 30-second periods.

\*The state 2 file was split in two parts for computational reasons; only half of the data is presented here.

**Table II.** Correlation coefficients (r) for the LTI index and the ID index with respect to the STI index

	Mean	Range
n	266	133 to 376
r(ID index, LTI index)	0.092	-0.141 to 0.315
r(STI index, LTI index)	0.124	-0.081 to 0.282

n = Number of 30-second periods recorded from the 11 newborn infants.

The difference  $t_i - t_{i-1}$  is weighted with a factor  $g_i$ , the value of which is primarily determined by the mean length of the two intervals (see Appendix II). For instance, the factor gi weights interval differences at 381 msec (157 beats/min) five times more strongly than at 500 msec (120 beats/min), whereas interval differences at 846 msec (71 beats/min) are weighted five times less strongly than at 500 msec. Interval differences below 381 msec are weighted with the same factor g<sub>i</sub> as applied at 381 msec in order to preclude that the beatto-beat differences at very high heart rates are overestimated. As noted in the previous section, heart rate data in the range below 375 msec were too few in number for experimental analysis, whereas the precision of the determination of interval differences is limited at very short intervals.

A period of 30 seconds was chosen for the calculation of the ID index, for the following reasons. Longer periods make it difficult to apply the index to fetal heart rate data during labor, in particular for the time periods between uterine contractions. Periods shorter than 30 seconds are not preferred because the sample size would then become too small, especially at lower heart rates. A period of 30 seconds means that cyclic variations with a frequency equal to or greater than 1 per minute can be accurately detected. This is important for the application of the long-term irregularity index (LTI index; for definition see Appendix III) synchronously with the ID index. Other authors 1. 17

also have preferred 30-second periods for the study of physiologic variables in fetuses and newborn infants.

#### **Artifact detection**

The heart rate data described before were also applied to establish criteria for the detection of artifacts. The interval-to-interval differences decrease when the interval length decreases, and vice versa. A larger time difference between the interval ti+1 and the preceding interval t<sub>i</sub> should, therefore, be accepted at longer interval lengths than at shorter interval lengths On the basis of the interval t<sub>i</sub>, limits have been set for interval ti+1 as formulated in an operational definition presented in Appendix IV. As a minimum, three intervals that qualify according to these standards must be present in succession before the intervals are accepted for processing, i.e., before RR interval differences are calculated. The limits for acceptance of ti+1 differ according to whether ti+1 is smaller or greater than ti. An acceleration of heart rate develops more slowly than does a deceleration. This phenomenon has been observed in the fetus1 as well as in the newborn infant (Jongsma, H. W., and van Geijn, H. P.: Unpublished observations). The ranges for acceptance of ti+1 are comparable with the ranges applied in commercial monitors (= last computed heart rate ± 20 beats/min]. Modanlou and associates12 reject beat-tc-beat heart rate changes that exceed 12 beats/min. Dalton and assoc.ates6 reject RR intervals which are reduced to less than 75% of the last interval or exceed the mean value of the three previous intervals by more than 50%.

#### Interval difference index and RR interval length

The definition of the ID index, based on the former analysis of the interquartile range of RR interval dizferences and interval length, should result in independence of the ID index from the interval length. To check this independence, correlation coefficients were calculated between the ID index and the median RR interval length. The median interval length was, like the ID index, calculated over 30-second periods. The analyzed heart rate data comprised the recordings of all the newborn infants obtained within one of the behavioral states, A, B, C. The correlation coefficients (r) between the ID index and the median RR interval length are given in Table I. For comparison, the r values of the median RR interval length and the shortterm irregularity index4 (STI index) are also given, calculated over the same 30-second periods. The r values for median RR interval length and ID index varied from -0.034 to 0.13, demonstrating a nearly complete independence for both parameters in the investigated neonatal behavioral states and in fetal recordings. Fig.

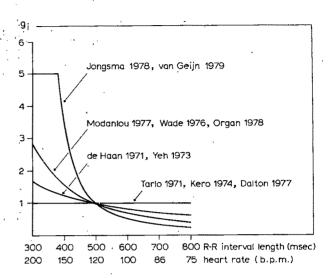


Fig. 3. The relationship between the RR interval length and the weighting factor gi (see text) for the various indices of beatto-beat heart rate variability.

2 shows the relationship between ID index and median RR interval length as found in state 2. The STI index, on the other hand, was strongly dependent on RR interval length (r = 0.67 to 0.73). Thus the correction in the ID index for RR interval length is satisfactory, at least on the average for a group of recordings. A stronger relationship between the ID index and the median RR interval length can exist in individual cases.

#### Interval difference index and long-term irregularity index

In a recent article, Laros and associates7 compared indices for short-term and long-term heart rate variability. The short-term irregularity index4 (STI index) and the long-term irregularity index4 (LTI index) demonstrated the least interdependence (median Kendall tau: 0.27) among the studied indices for fetal heart rate data. For a similar analysis of the interdependence between the ID index and the LTI index, the heart rate data obtained for each newborn infant in the various behavioral states have been combined. Table II gives the means and the ranges for the correlation coefficients between the ID index and the LTI index and between the STI index and the LTI index. Like the STI index, the ID index shows a very low sensitivity to the presence of heart rate fluctuations as measured by the long-term irregularity index.

#### Comment

On the basis of an analysis of the relationship between RR interval length and interquartile range of RR interval differences, the interval difference index (ID index) has been proposed that defines beat-to-beat.

Table III. Statistical parameters in use for quantitation of beat-to-beat heart rate variability

Author and year	Index	Fərraula	g*	Subject of study
de Haan et al.,⁴ 1971	Short-term irregularity (STI) index	$ \frac{\text{IQR of arctan}}{\left(\frac{t_1 - t_{1-1}}{2\overline{t_1}}\right)} $	$\frac{1}{\overline{t}_t}$	Human fetus
Yeh et al., <sup>5</sup> 1973	Differential index (DI)	SD over 30 seconds of $\frac{t_i - t_{i-1}}{2\overline{t}_i} \times 1,000$	$\frac{1}{\overline{t}_1}$	Human fetus
Tarlo et al.,º 1971 Kero, <sup>10</sup> 1974	RMSSD†	$\sqrt{\frac{\sum\limits_{i=1}^{n}(t_{i}-t_{i-1})^{2}}{n-1}}$ over n = 500 intervals		Human newborn infant
Modanlou et al., <sup>12</sup> 1977	Variability quantitation (VQ)	$\frac{1}{n}\sum_{i=1}^{n} f_i - f_{i-1} $ over 60 seconds	$\frac{1}{(\overline{t}_1)^2}$	Human fetus, newborn infant
Wade et al., <sup>11</sup> 1976 Organ et al., <sup>8</sup> 1978	Instantaneous variability	$\frac{1}{n}\sum_{i=1}^{n} \mathbf{f}_{i}  -  \mathbf{f}_{i-1} $ over 30 seconds	$\frac{1}{(\overline{t}_i)^2}$	Human fetus
Dalton et al., <sup>6</sup> 1977	Mean absolute beat-by- beat difference	$\frac{1}{2n} \sum_{i=1}^{n}  t_i - t_{i-1} $ over 0.25 to 120 min	1	Lamò fetus
Jongsma et al., <sup>14</sup> 1978 van Geijn, 1979 (present study)	Interval difference (ID) index	IQR over 3 $\mathbb{I}$ sec of $\frac{t_1 - t_{i-1}}{\left(\frac{\overline{t}_i - 320}{180}\right)^{1.1}}$	$\frac{1}{(\overline{t}_i-320)^{1.5}}$	Human fetus, newborn infant

IQR = Interquartile range. SD = Standard deviation.

heart rate variability and simultaneously takes into account the actual heart rate. The independence of this index from the heart rate allows the study of factors that influence beat-to-beat variability together with heart rate, e.g., distress, behavioral states, <sup>18</sup> and use of sedatives. <sup>19</sup>

The indices proposed in recent years to quantitate beat-to-beat heart rate variability are summarized in Table III. To compare the mathematical relationship between these indices, some of the symbols in the original formulas have been adapted to a more uniform notation. All indices contain as a factor the time difference between consecutive intervals  $(t_i - t_{i-1})$  or the difference in rate between consecutive heartbeats  $(f_i - f_{i-1})$ . The parameters of beat-to-beat variability in each index can be written approximately in the form  $g_i(t_i - t_{i-1})$ . This notation allows us to demonstrate the essential part of the relationship between the index and the interval length. The factor  $g_i$  is the weighting factor for the interval-to-interval differences. In the STI index,

g is the result of the transformation of  $(t_{i-1}, t_i)$  to polar coordinates and the choice of the argument as a parameter for beat-to-beat variations. Indices using differences of heart rate apply a  $g_i \approx 1(\div) \ \bar{t}_i{}^2$ . In the ID ir dex, as presented in the current study, the value of  $g_i$  is the result of an experimental analysis of neonatal heart rate data obtained under basal conditions.

Fig. 3 demonstrates how the value of  $g_i$  changes with the interval length for the various indices. To make comparison of the indices possible, the weighting factors in each index have been normalized to  $g_i = 1$  at  $t_i = 500$  msec. The range of the weighting factor  $g_i$  in the ID index is greater than that in the variability quantitation (VQ), <sup>12</sup> which, in turn, has a greater range than the comparable factor in the short-term irregularity index<sup>4</sup> (STI index).

According to the formula in Appendix I, the interval differences approach zero when the RR interval length decreases toward 320 msec. This reduction in interval-te-interval differences could have been anticipated

<sup>\*</sup>The weighting factor  $g_i$  is defined in such a way that the interval-dependent part of the indices can approximately be written as  $g_i(t_i - t_{i-1})$ .

<sup>†</sup>Root mean square of successive differences.

when the electrical and mechanical phenomena involved in the heartbeat are considered. When the heart rate changes, the effects in the electrocardiogram are primarily visible in the T-P time.20 The length of the PORST complex remains relatively constant. Likewise, an increase in heart rate is accompanied by a much greater shortening of diastole than of systole.21 Ventricular diastole corresponds, for the most part, with the T-P time; and systole, with the PQRST complex. Thus, variations in the total length of RR intervals are primarily due to variations in only a part of the interval length. The characteristic of the ID index is that variations in the interval length are divided by a function of the variable part of the RR interval  $(t_i - 320)$  instead of by the total interval length.

We are grateful to Professor Dr H. F. R. Prechtl and Dr C. A. Scholten for their generous provision of the heart rate data, which was recorded in the Department of Developmental Neurology, University of Groningen, The Netherlands. We also wish to thank Professor C. B. Martin for advice during preparation of the manuscript, and Ms. G. Theunissen for secretarial assistance.

#### REFERENCES

- 1. Martin, C. B.: Regulation of the fetal heart rate and genesis of FHR patterns, Semin. Perinatol. 2:131, 1978
- 2. de Haan, J., van Bemmel, J. H., Stolte, L. A. M., Janssen, J., Eskes, T. K. A. B., Versteeg, B., Veth, A. F. L., and Braaksma, J. T.: Quantitative evaluation of fetal heart rate patterns. II. The significance of the fixed heart rate during pregnancy and labor, Eur. J. Obstet. Gynaecol. Reprod. Biol. 3:103, 1971.
- 3. Sayers, B. McA.: Analysis of heart rate variability, Ergonomics 16:17, 1973.
- 4. de Haan, J., van Bemmel, J. H., Versteeg, B., Veth, A. F. L., Stolte, L. A. M., Janssens, J., and Eskes, T. K. A. B.: Quantitative evaluation of fetal heart rate patterns. I. Processing methods, Eur. J. Obstet. Gynaeccl. Reprod. Biol. 3:95, 1971.
- 5. Yeh, S-Y., Forsythe, A., and Hon, E. H.: Quantification of fetal heart beat-to-beat interval differences, Obstet. Gynecol. 41:355, 1973.
- 6. Dalton, K. J., Dawes, G. S., and Patrick, J. E.: Diurnal, respiratory, and other rhythms of fetal heart rate n lambs, Am. J. Obstet. Gynecol. 127:414, 1977.
- 7. Laros, R. K., Wong, W. S., Heilbron, D. C., Parer, J. T., Shnider, S. M., Naylor, H., and Butler, J.: A comparison of methods for quantitating fetal heart rate variability, Am. J. Obstet. Gynecol. 128:381, 1977.
- 8. Organ, L. W., Hawrylyshyn, P. A., Gocdwin, J. W., Milligan, J. E., and Bernstein, A.: Quantitative indices of short- and long-term heart rate variability, Am. J. OBSTET. Gynecol. 130:20, 1978.
- 9. Tarlo, P. A., Välimäki, I., and Rautaharju, P. M.: Quantitative computer analysis of cardiac and respiratory activity in newborn infants, J. Appl. Physial. 31:70, 1971.
- 10. Kero, P.: Heart rate variation in infants with the respiratory distress syndrome, Acta Paediatr. Scand., Supplement 250, 1974.
- 11. Wade, M. E., Coleman, P. J., and White, S. C.: A computerized fetal monitoring system, Obstet. Gynecol 48: . 287, 1976.
- 12. Modanlou, H. D., Freeman, R. K., and Braly, P.: A simple

- method of fetal and neonatal heart rate beat-to-beat variability quantitation: Preliminary report, Am. J. Obster. GYNECOL. 127:861, 1977.
- 13. de Haan, J., van Bemmel, J. H., Stolte, L. A. M., Veth, A. F. L., Janssens, J., and Eskes, T. K. A. B.: Trend detection in the fetal condition, Int. J. Obstet. Gynaecol. 10:202, 1972.
- 14. Jongsma, H. W., van Geijn, H. P., and de Haan, J.: The analysis of heart rate variability in the perinatal period, in Krause, W., editor: Computerdiagnostik in der Geburtsmedizin, Jena, 1978, Friedrich Schiller Universität, p. 249.
- 15. Burdick, J. A., and Scarbrough, J. T.: Heart rate and heart rate variability: An attempt to clarify, Percept. Mot. Skills **26:**1047, 1968.
- 16. Prechtl, H. F. R., Akiyama, Y., Zinkin, P., and Grant, D. K.: Polygraphic studies of the full-term newborn: I. Technical aspects and qualitative analysis, in McKeith, R., and Bax, M., editors: Studies in infancy. Clinics in Developmental Medicine, No 27, pp. 1-21, London, 1968, William Heinemann Medical Books, Ltd.
- 17. Anders, T. F.: The infant sleep profile, Neuropaediatrie 5:425, 1974.
- 18. van Geijn, H. P., Jongsma, H. W., de Haan, J., Eskes, T. K. A. B., and Prechtl, H. F. R.: Heart rate as an indicator of the behavioral state, Am. J. OBSTET. GYNECOL. 136:1061, 1980.
- 19. van Geijn, H. P., Jongsma, H. W., Doesburg, W. H., Lemmens, W. A. J. G., de Haan, J., and Eskes, T. K. A. B.: The effect of maternal diazepam medication during pregnancy or labor on the heart rate variability of the newborn infant, Eur. J. Obstet. Gynaecol. Reprod. Biol. 10:187, 1980.
- 20. Mücke, D., and Bartel, J.: Empfehlungen zur Auswertung und Beurteilung von Electrokardiogrammen im Kindesalter-Kurzgefasster programmierter Kurs. 2. Mitteilung. Zusammenstellung wichtiger Nomogramme, Z. Aertzl. Fortbild. (Jena) 70:494, 1976.
- 21. Caro, C. G., Pedley, T. J., Schroter, R. C., and Seed, W. A.: The mechanics of circulation, Oxford 1978, Oxford University Press.

#### Appendix I: Analysis of the relationship between the interval differences and the interval length

Each behavioral state, A, B, C, was analyzed separately. The values of the RR interval pairs  $(t_i, t_{i-1})$  of successive RR intervals were gathered. for which:

$$K-5 < \vec{t}_i < K+5$$
  $(K = 300,310,320 \dots 800 \text{ msec}).$   $\vec{t}_i = \frac{t_{i-1} + t_i}{2}$ 

The interquartile range (IQR) of the RR interval dif-

ferences (y<sub>i</sub>) was calculated over each interval K-5 <  $t_i <$  K + 5 of 10 msec:

$$y_i = IQR(t_i - t_{i-1})$$

Exceptions were made for the pairs  $(t_{i-1}, t_i)$ , with a  $\bar{t}_i$  value in the extreme lower and upper range because of the limited number of points available. The interquartile range of the RR interval differences was plotted against the mean interval length (see Fig. 1):

$$IQR(t_i - t_{i-1}), K.$$

For all neonatal behavioral states the experimental data were fitted to a function:

$$y_i = \bar{\alpha(t_i - t_o)^n}$$

As values for the exponent n at  $t_0 = 300$ , 320, and 340 msec were obtained:

t <sub>o</sub>	Α	В	C
(msec)	(state 1)	(state 2)	(state 3,4,5)
300	2.2	1.7	1.9
320	1.9	1.5	1.6
340	1.7	1.2	1.3

On the basis of the best least-squares fit and the chisquare scores, the following values were chosen for  $t_0$ and exponent n as a compromise:  $t_0 = 320$  msec, n = 1.5. Substituting these values gives the equation:

$$y_i = \alpha(\bar{t}_i - 320)^{1.5}$$

#### Appendix II: Definition of the interval difference index (ID index)

In the following formulas,  $t_i$  is the length in milliseconds of the RR interval i ( $i = 1, \ldots, n$ ). The ID index is defined as the interquartile range (over 30 seconds) of:

$$g_i(t_i - t_{i-1})$$
 (i = 2, ...n)

In this formula,  $g_i$  is a weighting factor, depending on the actual mean interval length  $(t_i)$ :

$$g_i = \left(\frac{180}{t_i - 320}\right)^{1.5} \text{ with } \overline{t}_i = \frac{t_{i-1} + t_i}{2}$$

For  $\bar{t}_i < 381$  msec:  $g_i = 5$ .

#### Appendix III: Definition of the long-term irregularity index (LTI index)

The LTI index<sup>4</sup> is defined as the interquartile range (over 30 seconds) of:

$$\sqrt{\frac{t_1^2+t_{1-1}^2}{2}} \quad (i=2,\ldots n)$$

#### Appendix IV: Artifact detection

In the first instance, those RR intervals are accepted which meet the criteria:

$$\begin{aligned} t_i - 0.43 \; (d_i) &< t_{i+1} < t_i + d_i \\ d_i &= t_i - 300. \end{aligned}$$

The minimum value for  $d_i$  is 20 msec. For final acceptance of  $t_{i+1}$  a minimum of three intervals that qualify to this formula must be present in succession.

# Pregnancy-specific $\beta_1$ -glycoprotein as a prognostic indicator in complications of early pregnancy

P. C. HO, M.B., B.S., M. R.C.O.G.\*
W. R. JONES, M.D., Ph.D., F.R.C.O.G.
Bedford Park, South Australia

Pregnancy-specific  $\beta_1$ -glycoprotein (SP-1) was measured by radioimmunoassay in patients admitted to the hospital with a clinical diagnosis of hemorrhage in early pregnancy. The results were compared with a normal range and were analyzed for their predictive value in determining prognosis. Six of the total study group of 54 patients were subsequently proved not to be pregnant and had SP-1 levels below 10  $\mu$ g/L, the lower limit of sensitivity for pregnancy detection. Twenty-nine patients had SP-1 levels below the normal range for pregnancy and all had an abnormal outcome (ectopic pregnancy or abortion). The SP-1 level was normal in 29 cases, of which 10 had an abnormal outcome and 19 continued normally beyond the twentieth gestational week. Low SP-1 levels were found in all of the abnormal and none of the continuing pregnancies and may be taken as predictive of an unsuccessful cutcome. (AM. J. OBSTET. GYNECOL.

UTERINE BLEEDING is a common complication in early pregnancy. In an Australian population, when admission to the hospital is required for this condition, 80% of patients subsequently abort. The early and accurate prediction of an unsuccessful pregnancy in this situation should lead to appropriate treatment without unnecessary delay, thereby avoiding inconvenience and psychological stress to the patient and reducing the costs of prolonged hospitalization. Various biochemical parameters such as urinary and plasma human chorionic gonadotropin (hCG),2-5 plasma human placental lactogen (hPL),4,6,7 urinary plasma estrogens,4,5 urinary pregnanediol,5 and plasma progesterone,4 alpha fetoprotein,4 C-reactive protein,8 and pregnancy zone protein<sup>9</sup> have been explored as prognostic indicators. The occurrence of false positive and false negative results with almost all of these tests has limited their value in aiding a clinical decision. Satisfactory results have been claimed for ultrasound in early pregnancy diagnosis but incorrect predictions still occur. 5, 10

From the Department of Obstetrics and Gynaecology, Flinders Medical Centre.

Received for publication February 1, 1980.

Revised May 8, 1980.

Accepted May 29, 1980.

Reprint requests: Professor W. R. Jones, Department of Obstetrics and Gynaecology, Flinders Medical Centre Bedford Park, 5042 South Australia.

\*Supported by the World Health Organization.

Pregnancy-specific  $\beta_1$ -glycoprotein (SP-1) is secreted by trophoblast<sup>11</sup> and is, therefore, a potential early indicator of placental survival. Schultz-Larsen and Hertz<sup>12</sup> reported, in threatened abortion after the ninth week of pregnancy, that serum SP-1 could be used to differentiate patients who subsequently aborted from those whose pregnancy continued. Jandial and associates<sup>13</sup> also reported good prediction with a single plasma SP-1 estimation. Discordant results, however, have been reported by other workers<sup>14</sup> and it was the aim of this study to reassess the prognostic value of serum SP-1 levels in complications of early pregnancy.

#### Material and methods

On admission 5 ml of venous blood for SP-1 assay was obtained from patients with a clinical diagnosis of threatened, missed, incomplete, or inevitable abortion. The assay results were not known to the clinician and did not influence patient management. The presence of a pregnancy was confirmed subsequently in all cases by one or more of the following criteria: (1) presence of chorionic villi in aborted or curettage material, (2) ultrasound evidence of intrauterine pregnancy, and (3) delivery of a fetus.

Blood samples were also taken for SP-1 assay from normal pregnant women who were between the sixth and seventeenth week of gestation and attending the antenatal clinic and also from normal subjects admitted for elective abortion. These samples were used to construct a normal range of SP-1 in early pregnancy.

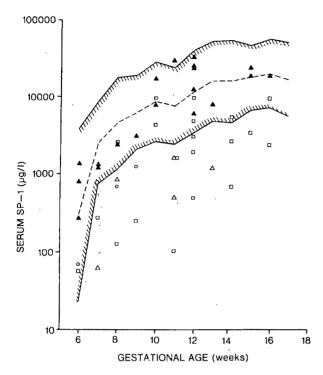


Fig. 1. Serum SP-1 levels in normal and complicated pregnancies. The upper and lower continuous lines represent the upper and lower limits of the normal range. The dotted line represents the mean of serum SP-1 levels in normal pregnancies. Δ: Threatened abortion but pregnancy continued. □: Threatened abortion and aborted subsequently. Δ: Nonviable pregnancy on admission, ο: Ectopic pregnancy.

Women with irregular menstrual periods and uncertain dates were excluded. All serum samples were stored at  $-20^{\circ}$  C until assay.

Serum SP-1 was determined by radioimmunoassay with a double-antibody technique. Pure SP-1 (provided by Dr. H. Bohn, Marburg) was iodinated by the chloramine-T method<sup>15</sup> with I<sup>125</sup>-labeled sodium iodide (Amersham). The reaction mixture was purified on a Biogel P6 column (10 mm by 10 cm). The labeled SP-1 was then stored at 4° C until use, when it was diluted to give a yield of 10,000 cpm for 0.2 ml. SP-1 standards (Beringwerke AG) were diluted to give concentrations ranging from 1.25 to 320  $\mu$ g/L. Anti-SP-1 (Dakopatts, Batch No. 018D) was used at a dilution of 1:50,000. Samples and standards were assayed in duplicate. The reaction mixture consisted of 0.1 ml of standard or sample, 0.2 ml of antibody, and 0.2 ml of labeled SP-1. After incubation at room temperature for 24 hours, 0.02 ml of donkey anti-rabbit globulin (Wellcome Research Laboratories) and 0.1 ml of normal rabbit serum (1:50 dilution) were added. The mixture was incubated at 4° C for a further 4 hours and centrifuged at  $2,000 \times g$  for 45 minutes at 4° C. The supernatant was discarded and the precipitate was counted. The per-

Table I. SP-1 concentration in normal pregnancy

Week of gestation	No. of subjects	Mean (μg/L)
6	8	301 (20-3,940*)
7	11	2,560 (750-8,690)
8	16	4,590 (1,180-17,950)
9	19	6,290 (2,080-18,980)
10	. 15	8,650 (2,660-28,150)
11	10	7,710 (2,430-24,490)
12	15	11,590 (3,360-39,950)
13	9	16,230 (4,920-53,530)
14	10	16,200 (4,710-55,680)
15	·7	18,040 (6,820-47,700)
16	25	20,460 (7,390-56,630)
17	8	17,420 (5,830-52,010)

<sup>=</sup>Normal range.

centage bound was calculated and a standard curve was pletted. Over 6 months, the sensitivity of the assay was  $1.25~\mu g/L$ , intra-assay variation was 6% and interassay variation was 9%. In a group of 100 normal nonpregnant control subjects, the assay gave a positive result up to a level of  $10~\mu g/L$ , which was, therefore, taken as the lower limit of practical sensitivity. Problems relating to the presence in pregnancy serum of varying amounts of the two forms ( $\alpha$  and  $\beta$ ) of SP-1 are minimized in the racioimmunoassay system since this predominantly measures "authentic" ( $\beta$ ) SP-1 in the presence of physiologic levels of SP-1.<sup>16</sup>

#### Results

One hundred fifty-three normal pregnancies and 62 complicated pregnancies were studied. As the distribution of serum SP-1 levels in normal pregnancy was skewed, the means and standard deviations (SD) for each gestational week were calculated after logarithmic transformation. The upper and lower limits of normal were taken as 2 SD from the mean. The serum SP-1 results in normal pregnancy are shown in Table I and Fig. 1.

Of the 62 complicated pregnancies, eight were excluded because of unreliable menstrual data. The results of the remaining 54 patients are shown in Fig. 1 and may be summarized as follows.

Nonpregnant group. Subsequent investigations in six patients showed that they were not pregnant. Uterine curettings revealed proliferative or menstrual endometrium and no chorionic villi. Serum SP-1 levels in these patients were less than  $10~\mu g/L$ .

**Ectopic pregnancies.** Three patients were subsequently proved to have tubal pregnancies. Laparotomy and unilateral salpingectomy were performed in all cases. The serum SP-1 levels were above  $10 \mu g/L$ ; two were below the normal range, while the third was normal.

Continuing pregnancies. In 19 patients, bleeding subsided after admission and the patients were discharged well. The serum SP-1 levels in this group were within the normal range for pregnancy. Three patients were subsequently delivered of normal live infants; the remaining 16 had progressed normally beyond 20 weeks' gestation at the time of this writing.

Pregnancies diagnosed as nonviable on admission. There were five patients in this category. All were treated with immediate evacuation of the uterus. The SP-1 levels were all above 10  $\mu$ g/L but below the lower limit of normal pregnancy.

Threatened abortion on admission and subsequently aborted. Twenty-one patients were diagnosed as having threatened abortions and were managed expectantly. Five proved to have a missed abortion on subsequent investigation and were treated with evacuation of the uterus. The remaining 16 aborted between 1 and 59 days after entering the study. All except one of the serum SP-1 values were below the mean for the corresponding gestational age and 12 were below the lower limit for normal pregnancy. There were no values below 10  $\mu$ g/L. In three of the nine patients who had a normal SP-1 level and aborted, a fetal heartbeat was present up to the time of abortion. One patient in the series became pregnant while attending the Fertility Clinic and had a serum SP-1 level below the normal pregnancy range at 6 weeks' gestation in the absence of vaginal bleeding or any other abnormality. She subsequently entered the study with a threatened abortion in the eleventh week of pregnancy. At that time a further serum SP-1 was still below the lower limit of normal and she aborted 2 days after admission to hospital.

In summary, all patients subsequently proved to be pregnant had a serum SP-1 value of greater than 10  $\mu$ g/L, while those with dysfunctional uterine bleeding had values below this level. A total of 65% of patients presenting with bleeding and a normal serum SP-1 result had continuation of pregnancy, while all those with a low SP-I value had an abnormal outcome (abortion or ectopic pregnancy).

#### Comment

The use of biochemical parameters to predict the outcome of pregnancies complicated by threatened abortion has proved disappointing. A single low level of plasma hCG is associated with abortion in 72% tc 92% of cases, while a normal hCG level is also associated with abortion in 10% to 30%.1.2, 4 The predictive accuracy of hPL is similar to that of hCG. A low plasma level of hPL is associated with abortion in 56% to 88% of cases, while a normal level is associated with abortion in 4% to 39%.4, 6, 7 Other parameters such as urinary and plasma estrogens,4.5 urinary pregnanediol,5 plasma progesterone,4 and alpha fetoprotein,4 C-reactive protein,8 and pregnancy zone protein9 are even less helpful. The incidence of false positive and false negative results significantly modifies the contribution each of those tests can make to the clinical management of threatened abortion.

The usefulness of ultrasound has also been explored in this context. Duff<sup>5</sup> reported that sonar examinations gave an accurate prognosis in 84% of cases of threatened abortion. Robinson, 10 using strict criteria of abnormality independent of menstrual or clinical histories, claimed that an absolute diagnosis could be made at the time of the first examination in all cases of missed abortion and hydatidiform mole and in just over half of the cases of blighted ovum, the remainder requiring a second and occasionally a third examination. However, he reported difficulty in anticipating fetal death in utero or impending abortion of a live fetus.

SP-1 is produced by the trophoblast.11 If there is trophoblastic dysfunction associated with abortion, the blood level of SP-1 may, therefore, be affected. For this reason, its use as a prognostic indicator in threatened abortion has been the subject of recent investigation. It was found that, after the ninth week of gestation, serum SP-1 measurement by immunoelectrophoresis was useful in differentiating continuing pregnancies from subsequent abortions.12 However, immunoelectrophoresis is insufficiently sensitive for use prior to this stage of pregnancy. Jandial and associates,13 using the more sensitive radioimmunoassay method, reported that a single plasma estimation of SP-1, although more useful than hPL in evaluating the outcome of complications of early pregnancy, had a false prediction rate of 24%. In addition, in four patients with a low SP-1 level, the pregnancies continued beyond the twenty-eighth week. If a decision had been made to evacuate the uterus in these patients based on the low SP-1 levels, the abortions would have been in error. The authors did not comment on the accuracy of the gestational maturity in their patients, and this may have influenced the interpretation of their results.

The results in the present study are more encouraging. Using a larger population of normal control subjects (153), we constructed a normal range for SP-1 that was somewhat wider than that of Jandial and associates,13 which was based on 67 patients. A total of 100% of our patients with a low serum SP-1 level had an abnormal pregnancy (ectopic pregnancy or a subsequent abortion). The serum SP-1 level was also consistently accurate in differentiating the pregnant from the nonpregnant state. However, in 35% of pregnancies which aborted subsequently, the serum SP-1 level was normal. Although most of these values were below the mean, an accurate prediction could not be made in these cases. A predictive error of 35% associated with a normal SP-1 value is explained to a certain extent by the varied etiology of spontaneous abortion. It is interesting, therefore, to note that the three patients aborting live fetuses had a normal SP-1 level. The detection of a low serum SP-1 value in one normal patient 5 weeks prior to the onset of vaginal bleeding and abortion suggests that trophoblastic dysfunction may be manifest very early in a pregnancy destined to abort subsequently.

Our study shows that the serum SP-1 level is a useful

prognostic indicator in complications of early pregnancy. None of the continuing pregnancies in this series had a low SP-1 level, which can, therefore, be taken as predictive of an abnormal outcome and may significantly influence the clinical management. Despite this, however, the usefulness of SP-1 measurements compares unfavorably with that of ultrasound. In most circumstances, ultrasound gives rapid and accurate results independent of maturity and is the single most helpful method for ancillary assessment of early pregnancy abnormalities. However, in equivocal cases, or in situations where ultrasound facilities are not readily available, a single estimation of the serum SP-1 level may be a valuable aid to management.

#### REFERENCES

- 1. Evans, J. H., and Beischer, N. A.: The prognosis of threatened abortion, Med. J. Aust. 2:165, 1970.
- 2. Joupilla, P., Tapanainen, J., and Huhtaniemi, I.: Plasma HCG levels in patients with bleeding in the first and second trimesters of pregnancy, Br. J. Obstet. Gynaecol. 86:343, 1979.
- Nygren, K. G., Johansson, E. D. B., and Wide, L.: Evaluation of the prognosis of threatened abortion from the peripheral plasma levels of progesterone, estradiol, and human chorionic gonadotropin, Am. J. Obstet. Gynecol. 116:916, 1973.
- Kunz, J., and Keller, P. J.: HCG, HPL, oestradiol, progesterone and AFP in serum in patients with threatened abortion, Br. J. Obstet. Gynaecol. 83:640, 1976.
- Duff, G. B.: Prognosis in threatened abortion: a comparison between predictions made by sonar, urinary hormone assays and clinical judgment, Br. J. Obstet. Gynaecol. 82:858, 1975.
- Vorster, C. Z., Pannall, P. R., and Slabber, C. F.: The prognostic value of serum human placental lactogen determinations in early pregnancy, Am. J. Obster. Gy-NECOL. 128:879, 1977.
- 7. Gartside, M. W., and Tindall, V. R.: The prognostic value of human placental lactogen levels in threatened abortion, Br. J. Obstet. Gynecol. 82:303, 1975.
- 8. Jones, W. R., and Ing, R. M. Y.: C-reactive protein in threatened abortion, IRCS Med. Sci. 4:263, 1976.
- 9. Beckman, G., Beckman, L., Mangusson, S. S., and von

- Schoultz, B.: The "pregnancy zone" protein and abortion, Acta Obstet. Gynecol. Scand. 53:177, 1974.
- Robinson, H. P.: The diagnosis of early pregnancy failure by sonar, Br. J. Obstet. Gynaecol. 82:849, 1975.
- Horne, C. H., Towler, C. M., Pugh-Humphries, R. G., Thomson, A. W., and Bohn, H.: Pregnancy-specific β<sub>1</sub>glycoprotein—a product of the syncytiotrophoblast, Experientia (Basel) 32:1197, 1976.
- perientia (Basel) 32:1197, 1976.
  12. Schultz-Larsen, P., and Hertz, J.: Pregnancy specific β<sub>1</sub>-glycoprotein in threatened abortion, Scand. J. Immunol. (Suppl.) 8:599, 1978.
- Jandial, V., Towler, C. M., Horne, C. H. W., and Abramovich, D. R.: Plasma pregnancy-specific β<sub>1</sub>-glyco-protein in complication of early pregnancy, Br. J. Obstet. Gynaecol. 85:832, 1978.
- 14. Grudzinskas, J. G., Gordon, Y. B., and Chard, T.: Assessment of fetal risk during early and late pregnancy using pregnancy specific β<sub>1</sub>-glycoprotein, in Lehman, F. G., editor: Carcino-embryonic Proteins, Amsterdam, 1979, vol. 2, Elsevier/North Holland Biomedical Press, p. 473.
- Greenwood, F. C., Hunter, W. M., and Glover, J. S.: The preparation of I<sup>131</sup>-labelled human growth hormone of high specific radioactivity, Biochem. J. 89:114, 1963.
- Teisner, B., Grudzinskas, J. G., Hindersson, P., Al-ani, A. T. M., Westergaard, J. G., and Chard, T.: Molecular heterogeneity of pregnancy specific β<sub>1</sub> glycoprotein: the effect on measurement by radioimmunoassay and electroimmunoassay, J. Immunol. Methods 31:141, 1979.

# Copper and ceruloplasmin activity in human amniotic fluid

WAI-YEE CHAN
JOANN RICHICHI
GUY E. GRIESMANN
WILLIAM CUSHING
O. RAY KLING
OWEN M. RENNERT
Oklahoma City, Oklahoma

The variation in the level of copper and ceruloplasmin oxidase activity in human amniotic fluid from 20 weeks' gestation to term was reported. The protein content of amniotic fluid decreased toward term. A definite decreasing trend of concentration of copper, expressed both as nanograms of copper per milliliter of amniotic fluid and nanograms of copper per milligram of protein, was also observed from midgestation toward term. Ceruloplasmin, on the other hand, demonstrated a significant increase from the period 20 to 38 weeks' gestation, with a subsequent decline after 38 weeks. (Am. J. Obstet. Gynecol. 138:257, 1980.)

AN INCREASING amount of emphasis has been placed upon the study of trace metals and their relationship to the infant's postnatal growth and development. Copper plays a significant role in the development of the central nervous system and maintenance of myelin structure. Numerous metalloproteins contain copper and function in aerobic metabolism (cytochrome oxidase), in collagen structure and synthesis (lysyl oxidase), in the mineralization of bone and formation of its organic matrix (ascorbic acid oxidase), and in the metabolism of neurogenic and biogenic amines (amine oxidases).<sup>1</sup>

The establishment of a defect in intracellular copper transport in Menkes' kinky hair disease<sup>2, 3</sup> and the abil-

From the Departments of Pediatrics, Biochemistry and Molecular Biology, and Obstetrics and Gynecology, University of Oklahoma Health Sciences Center.

Financial support was provided by Grants NoI-HR-7-2923 and HD12465-01 from the National Institutes of Health, and a Faculty Senate Award (to W. Y. C.) from the University of Oklahoma.

Received for publication January 8, 1980.

Revised April 22, 1980.

Accepted June 11, 1980.

Reprint requests: Owen M. Rennert, M.D., Department of Pediatrics, University of Oklahoma Health Sciences Center, P.O. Box 26901, Oklahoma City, Oklahoma 73190. ity to establish the diagnosis in at-risk infants have increased awareness of the functional significance of this trace metal during development. The clinical consequences of a deficiency of copper have been documented in the premature infant in association with intravenous hyperalimentation and the use of synthetic formulas. The composition of amniotic fluid often reflects fetal metabolic states. This study evaluated the diagnostic usefulness of the measurement of copper and ceruloplasmin concentration in amniotic fluid in the assessment of fetal growth and well-being.

#### Material and methods

Amniotic fluid. Specimens of amniotic fluid were obtained from pregnancies for therapeutic abortion, antenatal diagnosis of chromosomal disorders, hemolytic disease, and fetal lung maturity. Samples were obtained from 150 pregnancies of 20 weeks' gestation through term. To more clearly identify significant trends with regard to copper or ceruloplasmin concentration, the data have been assessed in terms of different stages of development. Thirty-one specimens were analyzed from pregnancies between 10 and 30 weeks' gestation, 32 specimens from 30 to 35 weeks' gestation, 60 specimens from 35 to 38 weeks' gestation, and 25 specimens from pregnancies of more than 38 weeks' gestation.

The specimens of amniotic fluid were obtained from

**Table I.** Concentrations of ceruloplasmin and copper in amniotic fluid

		Cerulop	olasmin	Cop			
Gestational age	N	units/gm protein	units/L	ng/mg protein	μg¦ail	Protein (mg/ml)	
20-30 weeks	31						
X		0.524	2.68	32.40	16.56	5.11	
SD		0.53	_	12.99		1.81	
30-35 weeks	32						
X		0.54	2.29	31.07	13.17	4.24	
SD		0.51		10.12		1.38	
35-38 weeks	60						
$\overline{\mathbf{X}}$		0.81	2.87	22.78	8.06	3.54	
SD		1.02	·	8.67	No.	1.23	
>38 weeks	25						
$\overline{\mathbf{x}}$		0.62	1.98	21.11	6.76	3.20	
SD		0.86	_	6.89	****	1.27	

individual patients, but none of the specimens included in this study was obtained from a single patient in a longitudinal fashion.

Samples were collected in a plastic syringe and immediately transferred to a plastic centrifuge tube.\* Cells were removed by centrifuging the samples of amniotic fluid at 2,000 g at 4° C in a Beckman J21C refrigerated centrifuge for 30 minutes, and the samples were then frozen and stored at  $-35^{\circ}$  C. Prior to analysis, the amniotic fluid was quickly thawed at  $37^{\circ}$  C.

Copper determination. Analysis for copper was performed with a Perkin-Elmer model 703 flameless atomic absorption spectrophotometer equipped with a Perkin-Elmer model HGA 500 graphite furnace and AS-1 autosampler. The following analysis program was followed: Drying at 110° C for 35 seconds, charring at 900° C for 30 seconds, atomization at 2.500° C for 10 seconds, at wavelength 324.7 nm. Ten microliters of amniotic fluid was used for each analysis. Triplicate analysis of each sample was performed. Standard solutions were made by appropriate dilutions of the 1,000 ppm copper reference standard.† Standards were run after every 10 samples, and blanks were run several times in order to assure a stable baseline. The reproducible sensitivity of this method for copper is 50 pg.

Ceruloplasmin oxidase activity assay. The oxidase activity of ceruloplasmin present in amniotic fluid was measured by its action on σ-dianisidine dihydrochloride according to the method of Schosinsky and associates. Human serum ceruloplasmin was purchased from Sigma Chemical Company and used as standard. Oxidase activity was expressed in units per gram of soluble protein. The protein content of the samples of

\*Falcon Plastics, San Francisco, California †Fisher Scientific Company, Pittsburgh, Pennsylvania. amniotic fluid was determined by the method of Lowry and associates.<sup>7</sup>

#### Results

Table I demonstrates that the concentration of copper, expressed in nanograms per milligram of protein, appears to decline from midgestation toward term. Although the values overlap throughout this time interval, a definite decreasing trend is observed. This trend in amniotic fluid is accompanied by a decreased concentration of protein as term is approached. Noteworthy is the fact that there is a significant increase in ceruloplasmin activity from 20 to 38 weeks' gestation, with a subsequent decline in the interval of 38 weeks' gestation or later. The data when expressed as micrograms of copper per deciliter or ceruloplasmin units per deciliter identify a similar pattern. The values for the concentration of copper are comparable to those described by Chez and associates.<sup>8</sup>

Diagnostic amniocenteses were performed for estimation of fetal maturity, Rh incompatibility, and other medical indications. The reasons for the diagnostic amniocenteses were varied and diverse, and no correlations were apparent with regard to the concentrations of copper and ceruloplasmin at the time the procedure was performed, nor with regard to the ultimate outcome of the pregnancy.

#### Comment

It has been documented that the onset of ceruloplasmin synthesis occurs at 4 to 5 weeks' gestation in the fetal liver. Adult stores of copper are exceeded in fetal liver at a gestational age of 10 to 12 weeks and subsequently decline throughout gestation to achieve their postnatal levels. The work of several investigators9 has demonstrated that ceruloplasmin is detectable in the serum of the fetus at 61/2 weeks' gestation, and subsequently rises to the period of 27 weeks' gestation to term, at which time it reaches concentrations of 4.6 to 16.5 mg/dl. It has been demonstrated that estrogen stimulates the synthesis of ceruloplasmin in the fetus. 10 To assess the potential functional significance of levels of copper in amniotic fluid, investigation of ceruloplasmin activity in amniotic fluid has also been performed. No information is available at present as to the origin of ceruloplasmin in amniotic

Previous reports on the copper content in amniotic fluid expressed the concentration of this trace element in terms of micrograms per deciliter.<sup>8, 11–13</sup> Because of the increasing volume of amniotic fluid as gestation progresses, expressing the copper content in the fluid with respect to unit weight of soluble protein may be

more representative than with respect to unit volume. Even though in this study the values for copper concentration were comparable to those described previously, the trend of change was more obvious when they were expressed in terms of micrograms of copper per milligrams of protein.

Investigations by others have documented the presence of lysozyme, transferrin, immunoglobulins, and a number of enzymes in human amniotic fluid. A low-molecular-weight zinc peptide has also been isolated which shows antimicrobial activity. However, ceruloplasmin activity in amniotic fluid has never been

investigated. The present report establishes a baseline with regard to the concentrations of copper and ceruloplasmin in amniotic fluid.

A recent report indicated that the concentration of copper in the amniotic fluid of the mother of a patient with Menkes' disease was four times the normal mean value at term. <sup>16</sup> Thus, the possibility exists that changes in the amniotic fluid concentration of copper or cerulo-plasmin may be useful diagnostic tools for evaluating fetal growth and development and assessing copper homeostasis in the developing fetus and embryo.

#### REFERENCES

- Underwood, E. J.: Trace Elements in Human and Animal Nutrition, ed. 4, New York, 1977, Academic Press.
- Chan, W. Y., Garnica, A. D., and Rennert, O. M.: Metalbinding studies of metallothioneins in Menkes' kinky hair disease, Clin. Chim. Acta 88:221, 1978.
- Chan, W. Y., Garnica, A. D., and Rennert, O. M.: Cell culture studies of Menkes' kinky hair disease, Clin. Chim. Acta 88:495, 1978.
- Perlman, M., Ramadan, T., Chan, W. Y., and Rennert, O. M.: Serial copper and ceruloplasmin values in serum of preterm infants, Clin. Res. 27:799A, 1979.
- Seely, J. R., Humphrey, G. B., and Malter, J. B.: Copper deficiency in premature infants fed an iron-fortified formula, N. Engl. J. Med. 286:109, 1972.
- Schosinsky, K. H., Lehmann, H. P., and Beeler, M. F.: Measurement of ceruloplasmin from its oxidase activity in serum by use of o-dianisidine dihydrochloride, Clin. Chem. 20:1556, 1976.
- Lowry, O. H., Rosebrough, N., Farr, A. L., and Randal, R.: Protein measurement with the folin phenol reagent, J. Biol. Chem. 193:265, 1951.
- Chez, R. A., Henkin, R. I., and Fox, R.: Amniotic fluid copper and zinc concentrations in human pregnancy, Obstet. Gynecol. 521:125, 1978.
- Gitlin, D., and Biasucci, A.: Development of γG, γA, γN, β1c/β1a, C'1 esterase inhibitor, ceruloplasmin, transferrin, hemofuscin, hepatoglobulin, fibringen, plasmino-

- gen, αl-antitrypsin, orosomucoid, β-lipoprotein, α2-macroglobulin and prealbumin in the human conceptus, J. Clin. Invest. 48:1433, 1969.
- Gitlin, D., and Gitlin, J. D.: Fetal and neonatal development of human plasma proteins, in Putnam, F. W., editor: The Plasma Proteins, vol II, New York, 1975, Academic Press, pp. 264-319.
- Chan, W. Y., Perlman, M., Seale, T. W., Kling, O. R., and Rennert, O. M.: Variation of trace element contents of human amniotic fluid with gestation, Pediatr. Res. 13:356, 1979.
- Henkin, R. I., Marshall, J. R., and Meret, S.: Maternalfetal metabolism of copper and zinc at term, Am. J. OBSTET. GYNECOL. 110:131, 1971.
- Nusbaum, M. J., and Zettner, A.: The content of calcium, magnesium, copper, iron, sodium, and potassium in amniotic fluid from eleven to nineteen weeks' gestation, Am. J. Obstet. Gynecol. 115:219, 1973.
- 14. Sutcliffe, R. G.: The nature and origin of the soluble protein in human amniotic fluid, Biol. Rev. 50:1, 1975.
- Schlievert, P., Johnson, W., and Galask, R. P.: Bacterial growth inhibition by amniotic fluid. VI. Evidence for a zinc-peptide antibacterial system, Am. J. Obstet. Gynecol. 125:906, 1976.
- Grover, W. D., Johnson, W. C., and Henkin, R. I.: Clinical and biochemical aspects of trichopoliodystrophy, Ann. Neurol. 501:65, 1979.

## Epidural morphine analgesia in second-trimester induced abortion

FLORELLA MAGORA, M.D.
Y. DONCHIN, M.D.
D. OLSHWANG, M.D.
J. G. SCHENKER, M.D.

Jerusalem, Israel

Epidural administration of 2 mg of morphine to 16 patients who were undergoing induced abortion in the second trimester of pregnancy abolished labor pains in 10 of them within 10 to 20 minutes after treatment was begun. The pain did not recur until the abortion process started, somet mes hours later. In one patient, the relief of pain was achieved with an additional top up dose of 1 mg 15 minutes later. In the other five patients in whom the morphine had no appreciable effect, the addition of 4 ml of 0.5% bupivacaine hydrochloride, also injected epidurally, successfully abolished pain. Because of the beneficial and prolonged action of morphine, as well as the lack of side effects, continuous epidural analgesia with low doses of it—supplemented, if necessary, with small quantities of bupivacaine—is effective for treatment of labor pains in induced abortion in the second trimester of pregnancy. The involvement of the anesthetist from the very beginning of the induction procedure is highly recommended. (Am. J. Obstet. Gynecol. 138:260, 1980.)

INDUCED ABORTION in the second trimester of pregnancy by means of hypertonic solutin of urea or intraamniotic prostaglandins1 is associated with severe and prolonged pain, similar to that experienced in childbirth. Since the welfare of the fetus does not come into consideration in these patients, there is no contraindication to the use of narcotic drugs in order to control the pain. However, the problem of untoward effects of the narcotic analgesics on the mother still remains. Furthermore, in spite of high doses of narcotic drugs, the pain often persists. Continuous lumbar epidural anesthesia is safe and efficient and is commonly used to attenuate labor pains.2, 3 Recently, it was demonstrated that morphine in minimal quantities injected into the subarachnoid or epidural space is a potent analgesic in animals4-6 as well as in man.7-9 The suggestion was made that morphine exerts its effect by direct action on

From the Department: of Anesthesiology and Obstetrics and Gynecology, Hadassah University Hospita! and Hebrew University-Hadassah Medical School.

Received for publication December 3, 1979.

Revised April 24, 1930.

Accepted June 11, 1980.

Reprint requests: Florella Magora, M.D., Department of Anesthesiology, Hadassah University Hospital, Ein Karem, Jerusalem, Is-ael. the specific opiate receptors present in the posterior horn of the spinal cord.<sup>4-6</sup>

In animals, intrathecal morphine did not cause adverse tissue reactions on the spinal cord, <sup>10</sup> and, in man, no side effects, such as hypotension, respiratory depression, or behavioral changes, were observed, <sup>7. 8</sup> except after high doses of pethidine. <sup>12</sup>

Epidural analgesia by means of the administration of morphine may be a useful treatment for pain associated with second-trimester induced abortion. Our observations and experience in 16 patients are presented in this study.

#### Patients and methods

Sixteen women who ranged in age between 17 and 41 years were admitted to the Department of Obstetrics and Gynecology for induction of abortion in the second trimester of gestation. The indications for termination of pregnancy were German measles in the first trimester in five patients, Down's syndrome in one, and psychosocial reasons in ten.

All patients were in good general health. Abortion was induced by intra-amniotic injection of hypertonic 30% urea in 12 patients and with prostaglandin F<sub>2</sub> in four. Amniocentesis was performed in all patients, and after as much amniotic fluid as possible had been withdrawn, a volume of urea was instilled which was 200 te

Table I. Clinical data on the patients

·		Analge	sia for labor pain		Anesthesia	Time to abortion (min)
	Gestational age (wk)	Morphine (mg)	Bupivacaine hydro- chloride, 0.5 % iml)	Results	for removal of retained placenta	
1	21	2	<u> </u>	Good	None	240
2	20	2		Good ·	General	300
3	23	2 + 1	4	Good after bupivacaine	None	320
4	22	2 + 1		Fair	General	60
5	20	2 + 1	4	Good after bupivacaine	None	180
6	21	2		Good	None	480
7	22	2	•	Good	None	210
8	20	2	•	Good	None	120
9	19	2		Good	Regional	180
. 10	21	2		Good	Regional	240
11	21	2	•	Good	None	40
12	18	2		Good; top up with morphine after 9 hr	None	660
13	18	2		Good	None	300
14	21	$\frac{1}{2} + 1$	3	Good after bupivacaine	None	540
15	- 22	2 + 1	· 3	Good after bupivacaine	None	420
16	21	2 + 1	4 .	Good after bupivacaine	None	460

220 ml more than the amount of amniotic fluid removed. In the patients who received prostaglandins, only 8 ml of a 0.5% solution was given. Because spontaneous uterine contractions did not occur within 12 tc 24 hours in four patients, oxytocin in gradually increasing doses was infused intravenously in these women.

When contractions began, the patient was taken to a special unit in the labor room. After the procedure of analgesia with epidural morphine had been explained to the patient, informed consent was obtained in each instance. A Tuohy epidural needle was introduced at the second or third lumbar interspace, and 2 mg of morphine sulfate, 0.1%, in 8 ml of normal saline solution, was injected into the epidural space. A catheter was left in place for repeated doses. Continued pain in six patients necessitated the administration of an additional dose of 1 mg of morphine, 0.1%, 15 minutes after the initial injection; in five women this had to be followed by 3 or 4 ml of bupivacaine hydrochloride, 0.5%. Intravenous infusion of glucose, 5%, instituted at the beginning of the epidural analgesia, was maintained throughout. The patients did not receive systemic medication and were kept fasting during the entire period of treatment. Blood pressure, pulse rate, respiration, and the behavior of the women were continuously monitored. The intensity of pain was evaluated according to the patient's subjective report. Each woman had to grade the analgesia as either good or fair, or had to ask for narcotics.

#### Results.

Induction of abortion was successful in all patients. The injection of 2 mg of morphine into the epidural space abolished labor pains in 10 of the 16 women

within 10 to 20 minutes after administration was begun. Relief of pain continued until the time of abortion, which occurred between 40 minutes and 11 hours after the instillation of the epidural morphine (Table I). In one patient, the morphine was topped up 9 hours after the first administration, with similar good effect. In the other six patients, because there was little or no relief of pain after the injection of morphine, a further dose of 1 mg was added by way of the epidural catheter, without appreciable effect. Therefore, five of the patients received, in addition to the morphine, 3 or 4 ml of bupivacaine, 0.5%, which suppressed the pain of the contractions until delivery of the stillborn fetus (3 to 7½ hours) (Table I).

All women were awake and quiet during the entire period of labor and reported that, although they could sometimes feel the contractions, they had no sensation of pain.

There were no changes in blood pressure or pulse rate, nor were there any signs of systemic effects of morphine, such as respiratory or cerebral depression.

The intrauterine manual exploration for retained fragments and curettage after abortion of the fetus and expulsion of the placenta did not require additional anesthesia in 12 of the patients; but two patients were under general anesthesia when the procedures were performed, regional anesthesia was applied in the other two by adding 4 ml of bupivacaine hydrochloride, 0.5%, through the epidural catheter (Table I).

#### Comment

In patients with an intact nerve supply to the uterus, the contractions of established labor are associated with pain. Stretching of the cervix when dilation begins,.

ischemia of the myometrial fibers during uterine contraction, and distention of and pressure on the muscles and ligaments of the lower birth canal, vulva, and perineum are all factors that contribute to the production of labor pain.2, 3, 12 An analysis of the mechanism of pain during labor reveals that all these factors are at work regardless of whether the fetus is delivered at term or in the second trimester of gestation. In addition, the other physiologic changes seen in term pregnancy, such as elevation of the diaphragm, changes in cardiac output due to regional distribution of blood, caval compression in the dorsal position, increased pressure, and slow intragastric emptying time, all apply to the women scheduled for abortion in the second trimester of pregnancy. True, the welfare of the baby in these cases is not relevant, so that after abortion has been induced, the usual practice in many places is to keep the patient in the gynecologic ward and occasionally administer narcotics for relief of pain and give some measure of sedation. However, the pain may persist in spite of the parenteral drug therapy. The uterine contractions in induced abortion are often prolonged, and the gravid patient is altogether unprepared for delivery. For many, it is the very unfortunate experience of a first pregnancy.

In textbooks on obstetric anesthesia, the treatment of pain in induced abortion in the second trimester is not discussed separately. Besides the physiologic changes of pregnancy, these patients present specific psychological problems which sometimes may have far-reaching, adverse effects in future pregnancies. For these reasons, it is our opinion that the application of oostetric analgesia is as important in these patients as in normal deliveries.

The patients in the current study were all treated in a special unit of the delivery room, and all received epidural analgesia. Morphine alone, injected into the epidural space, relieved labor pains in 10 of the 16 patients in this series. The effect was prolonged and lasted until the actual time of abortion had set in, which occurred between 40 minutes and 11 hours after analgesia was begun. No further anesthesia was required during intrauterine exploration by the surgeon in seven of the patients. There were no signs of sympathetic block or any other side effects. However, it was disappointing that the supplementary increment of epidural morphine (1 mg) failed to abolish the pain in five instances.

Of interest was the fact that in cases in which morphine failed, the addition of small amounts of bupivacaine (3 to 4 ml of 0.5% solution) resulted in the relief of pain for prolonged periods in all instances, no matter whether this drug was given to alleviate the pain of uterine contractions or that associated with intrauterine examination. It is possible that the prolonged beneficial effect of a small amount of bupivacaine was due to the fact that the progress of a small-sized fetus (as in the second trimester of pregnancy) may have caused less pressure on the neighboring muscles and ligaments during uterine contraction, thus producing less pain.

In conclusion, involvement of the anesthetist from the very beginning of the treatment in induced labor in the second trimester of pregnancy is recommended. The epidural morphine was effective in providing analgesia in 63% of patients who had painful uterine contractions associated with therapeutic abortion.

#### REFERENCES

- Yarkoni, S., Malaach, D., and Schenker, J.: Induced abortions and their complications, Harefush 96:603, 1979.
- Crawford, J. S.: Principles and practice of obstetric anaesthesia, ed. 3, London, 1972, Blackwell Scientific Publications, chap. 4, p. 138.
- 3. Shnider, S. M., and Moya, F.: Experience with regional anesthesia for vaginal delivery, in The Anesthesiologist, Mother and Newborn, Baltimore, 1974, Williams & Wilkins Co., chap. 4, p. 38.
- 4. Yaksh, T. L., and Rudy, T. A.: Analgesia mediated by a direct spinal action of narcotics, Science 192:1367, 1976.
- 5. Yaksh, T. L., and Rudy, T. A.: Studies on the direct spinal action of narcotics in the production of analgesia in the rat, J. Pharmacol. Exp. Ther. 202:411, 1977.
- 6. Yaksh, T. L., Frederickson, C. A., Huang, S. P., and Rudy, T. A.: In vivo comparison of receptor populations acted upon in the spinal cord by morphine and pen-

- tapeptides in the production of analgesia, Brain Res. 148:516, 1978.
- Wang, Y. K.: Soulagement de la douleur par injection intrathécale de sérotonine ou de morphine (résumé), Ann. Anesthesiol. Fr. 19:371, 1978.
- Behar, M., Magora, F., Olshwang, D., and Davidson, J. T.: Epidural morphine in treatment of pain, Lancet 1:527, 1979.
- Wang, J. K., Nauss, L. A., and Thomas, J. E.: Pain relief by intrathecally applied morphine in man, Anesthesiology 50:149, 1979.
- 10. Wang, J. K.: Analgesic effect of intrathecal administration of morphine, Reg. Anesth. 2:3, 1977.
- 11. Bonica, J. J.: Principles and Practice of Obstetric Analgesia and Anesthesia, chap. 5, The nature of pain of parturition, Philadelphia. 1972, F. A. Davis Company, p. 104.
- Scott, D. B., and McClure, J.: Selective epidural analgesia, Lancet 1:1410, 1979.

# Hemodynamics in patients with severe toxemia during labor and delivery

TERENCE D. RAFFERTY, M.D. RICHARD L. BERKOWITZ, M.D.

New Haven, Connecticut

Three patients with severe pre-eclampsia-toxemia were studied with thermodilution tip pulmonary artery catheters. All patients were delivered by cesarean section with general anesthesia and endotracheal intubation. The left ventricular stroke work indices (LVSWI) of these patients were higher than those of normal nonpregnant subjects. There was no evidence of myocardial depression in terms of either cardiac index or the LVSWI-pulmonary capillary wedge pressure (Frank-Starling) relationship. Pulmonary arteriolar resistance (PAR) was found to be within or below the normal nonpregnant range, suggesting that in severe toxemia the pulmonary vasculature is not involved in a primary vasospastic process. At delivery a rise in cardiac index (CI) and mean pulmonary capillary wedge pressure (PCWP) occurred. The PCWP was higher in the postpartum period than prior to delivery. This was felt to represent an increase in circulating blood volume. The therapeutic significance of these findings is discussed. (AM. J. DBSTET. GYNECOL. 138:263, 1980.)

PRE-ECLAMPSIA-TOXEMIA (PET) is a vasospastic disorder which is characterized by an increase in systemic arteriolar resistance<sup>1</sup> along with a decrease in circulating blood volume.2 It has been reported that cardiac output is within normal limits for pregnancy in toxemic patients,1 which suggests a compensatory increase in left ventricular work to offset the elevated peripheral resistance. The magnitude of this response, however, is unknown. In view of the systemic nature cf PET, it is not unreasonable to suppose that pulmonary hypertension might be an integral part of the syrdrome. The extent to which the pulmonary vasculature is involved in the disease process is also unknown. The importance of intravascular volume replacement in the management of toxemic patients continues to be a source of controversy.3, 4 These basic questions concerning the consequences of severe toxemia on the maternal circulatory system remain unanswered.

Until fairly recently, it has not been possible to obtain sophisticated central hemodynamic data at the bedside.

From the Departments of Anesthesiology and Obstetrics and Gynecology, Yale University School of Medicine.
Received for publication February 26, 1979.
Revised February 22, 1980.
Accepted May 29, 1980.

Reprint requests: Richard L. Berkowitz, M.D., Department of Obstetrics and Gynecology, Yale Universit; School of Medicine, 333 Cedar St., New Haven, Connecticut 06510. With the advent of thermodilution-tipped, flow-directed pulmonary artery catheters, however, this is no longer the case. In this study, Swan-Ganz (SG) catheters were utilized not only as a guide to therapy but also as investigational tools in an attempt to clarify the central hemodynamics of severe PET in the period surrounding delivery.

#### Clinical material

Three patients, ranging in age from 15 to 28 years, were studied on the high-risk obstetrics service of the Yale-New Haven Hospital (Table I). All had severe toxemia as defined by an acute hypertensive episode occurring in the last trimester, with admission blood pressures in excess of 170/120 mm Hg and proteinuria (3+ to 4+). None of these patients had an antecedent history of hypertension. One of the three patients (B. J.) had eclampsia, and none was in spontaneous labor at the time of admission. They were all treated with an intravenous loading dose of 4 gm of magnesium sulfate, followed by a continuous infusion of 1 gm/hour. Two of the three patients (J. L. and M. C.) received oxytocin stimulation for 4 to 6 hours.

All three patients were delivered by cesarean section with general anesthesia following a rapid induction-intubation sequence. Induction of anesthesia was accomplished with intravenous thiopental (1.5 to 3 mg/kg) immediately followed by endotracheal intubation facilitated by intravenous succinylcholine (0.5 to 1 mg/kg). Ventilation was controlled with 60% nitrous

Table I. Demographic data

Patient	Age	Height	Weight (pounds)	BSA	Parity	Con-dition	Admission BP (mm Hg)	· . Fetus
J. L.	25	5'2"	280	2.2	$P_0G_3AB_2$	Pre-e:lampsia	180/120	Term, Ap 4,6, BW 2,830 gm, baby lived 1 day (metastatic neuroblastoma)
М. С. В. J.	28 15	5′6″ 4′11″	156 94	1.8 1.29	$P_1G_3AB_1$ $P_0G_1$	Pre-e <lampsia Eclampsia</lampsia 	198/122 186/124	31 wk, Ap 8,6, BW 1,140 gm 33 wk, Ap 7,8, BW 1,800 gm

BP: Blood pressure; Ap: Apgar score; BW: birth weight.

oxide and 40% oxygen. After delivery of the baby supplementary anesthesia was provided by halothane (0.5%) or intravenous morphine 0.05 to 0.1 mg/kg). Further muscle relaxation was accomplished by additional succinylcholine.

The antepartum rate of crystalloid fluid administration is shown in Tables II, III, and IV. Two patients also received 25 gm of salt-poor albumin (SPA) in the postpartum period. Magnesium sulfate infusion was maintained for at least 24 hours following delivery. All patients had received or were receiving hydralazine therapy during the period studied.

#### Methods

Radiopaque flow-directed catheters (Swan-Ganz catheter, Model No. 934-131-7F, Edwards Laboratories) were inserted with local anesthesia in the antepartum period via the right internal jugular vein, and waveform characteristics and intravascular pressures were used as guides to placement. Catheter position was confirmed by chest roentgenography. A Teflon catheter (No. 20 angiocath) was inserted percutaneously into the radial artery of each patient. Intravascular pressures were recorded with Bentley transducers (No. 800) calibrated with mercury. The zero reference point was the middle of the anteroposterior chest. All determinations were made at endexpiration. Cardiac output was measured in duplicate by the thermodilution method with a cardiac output analogue computer (Edwards Laboratories No. 95100). The antepartum measurements were determined between uterine contractions without the influence of oxytocin stimulation. During the antepartum period measurements were obtained with the patient lying on the left side to eliminate obstruction of venous return and aortic flow by the gravid uterus. During the cesarean sections the right hip was elevated by a blanket roll for the same reason. Measurements were obtained 60 and 30 minutes prior to cesarean section. At delivery two sets of determinations were performed. Hemodynamic variables were also determined hourly for 9 hours after delivery.

All values for cardiac output, stroke work, and the resistances were expressed as indices in order to allow for variations in body size. Cardiac index, left ventricular stroke work index (LVSWI), total peripheral resistance, pulmonary arteriolar resistance, and body surface area (BSA) were calculated according to the formulas in Table V.

#### Results

Left ventricular function. The normal range of the LVSWI in pregnancy is not known. Each of our three patients had indices which were well above the normal resting nonpregnant range (56.4 = 3.6 gm m/sq m).<sup>5, 6</sup> When LVSWI, expressed as a function of mean pulmonary capillary wedge pressure (PCWP) (Frank-Starling relationship), was examined in order to assess left ventricular function, all data points fell within or above the normal range<sup>7</sup> (Fig. 1).

Pulmonary vasculature—all periods. The normal arteriolar resistance in pregnancy is not known. The pulmonary arteriolar resistance of our patients was consistently within or below the normal nonpregnant range (2.0  $\pm$  0.9 mm Hg L<sup>-1</sup> sq m).<sup>5, 8</sup> No simultaneously determined pulmonary arterial diastolic pressure (PADP)– $\overline{PCWP}$  gradient was in excess of 7 mm Hg in any patient.

Antepartum period. The pulmonary arterial systolic, diastolic, and mean pressures and the PCWPs were higher post partum than antepartum. Mean and diastolic systemic arterial pressure and heart rate were lower post partum (Tables II, III, and IV).

**Delivery period.** The delivery period, as compared with the antepartum period, was marked by a rise in systemic arterial blood pressure, pulmonary arterial systolic and mean pressures, and PCWP. A rise in cardiac index and stroke work index also occurred (Tables II, III, and IV).

**Postpartum period.** Diastolic systemic arterial blood pressure and left ventricular stroke work indices were lower post partum than during delivery. Total peripheral resistance also fell post partum (Tables II, III, and IV).

#### Comment

Left ventricular function. Because of the wide range of BSAs the cardiac outputs and other related variables of our patients were expressed as indices. Quantitative comparison of these data with those of healthy nonpregnant patients was possible because the inclusion of BSA measurements in the original reports permitted appropriate adjustments to be made. 6. 8. 9 This type of reanalysis of the studies on pregnant women published by Ueland and Hansen<sup>10</sup> and Assali and associates' could not be performed. When compared with norma. resting, nonpregnant individuals; 6.8,9 the patients with PET demonstrated elevations of cardiac index of approximately 50%.

Cardiac work is increased during pregnancy in order to maintain the elevation in cardiac output which normally occurs. In PET demands on the heart are even greater because systemic vascular resistance is increased. Determination of left ventricular stroke work requires a knowledge of the stroke volume index (cardiac index divided by heart rate) as well as the differences between mean arterial pressure and PCWP. Values for these indices in normal pregnant patients have not been published; therefore, comparisons were made with normal, nonpregnant control subjects. The values for LVSWI in the PET patients were well above the normal nonpregnant resting range.5. 6. 8 Although a cardiomyopathy has been reported in association with PET, there was no evidence of impaired contractility in terms of the LVSWI-PCWP relationship in our pa-

Pulmonary vasculature. Our data, when compared to those of healthy nonpregnant control subjects. revealed no increase in pulmonary arteriolar resistance.8 9 Values during normal pregnancy were not available for comparison. Furthermore, the gradient between the pulmonary artery diastolic pressure and PCWP was within normal limits.11 These observations suggest that in PET the pulmonary vasculature, unlike its systemic counterpart, is not involved in a primary vasospastic process that is hemodynamically significant.

Central intravascular pressures. Swan-Ganz catheterization permits the ongoing determination of pulmonary artery pressure and PCWP. The latter is an intravascular measurement which, in the absence of mitral valve disease, reflects left ventricular enddiastolic volume. A change in ventricular wall compliance may alter the measured intravascular pressure. In our study this variable was arbitrarily assumed to be constant. Therefore, central intravascular pressures were taken to represent left ventricular end-diastolic volume and to reflect changes in circulating blood volume as well as the functional state of the myocardium.

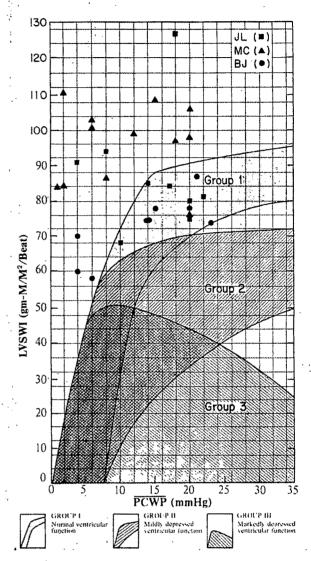


Fig. 1. This graph distinguishes between three levels of ventricular competence. Each of our three patients demonstrated excellent ventricular function by these criteria, even in the presence of markedly elevated PCWP values. (Modified from Ross, J., Jr., and Braunwald, E.: The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotensin, Circulation 29:739, 1964.)

Antepartum period. The reported blood volume deficits in PET cover a wide spectrum. Chesley12 stated that in severe disease the plasma volume may decrease as much as 30% to 40%. In this series of toxemic patients the highest PCWP recorded immediately following the insertion of a Swan-Ganz catheter in the antepartum phase was 5 mm Hg. One patient had an initial value of 2 mm Hg. All patients were subsequently vigorously hydrated. In nonpregnant patients the normal range of PCWP is 7 to 15 mm Hg.8 Values below the lower figure are consistent with diminished cardiac preload.

Table II. Measured and derived variables in Patient J. L.\*

	Time											
Variable	1 ½ hr AP	l hr AP	½ hr AP	Intubation	Delivery	1 hr PP						
BP (S/D/M)	140/96/110	150/100/117	160/100/120	240/140/173	180/100/127	180/70/107						
HR`	104	102	120	140	110	124						
PA (S/D/M)	18/5/9	21/8/12	25/12/16	42/18/26	36/13/24	30/13/19						
PCWP	4	' 8	10	18	21	16						
CO	14.4	14.2	12.0	18.4	16.4	_						
CI	6.5	6.4	5.4	8.3	7.4	_						
SVI	62.9	63.2	45.4	59.7	67.7							
LVSWI	90.7	93.8	68.0	126.7	14.1	_						
PAR	0.76	0.92	1.1	0.95	0.53	_						
TP¸R	16.8	18.1	22.0	20.8	23.3	_						
Fluids:				•								
$D_5/W$ and $D_5/RL$ (ml)	850	800	300	. –	****	500						
SPA (gm)		_	Broad	_	***	_						
Urine output (ml)	30	20	30	80		120						
EBL (ml)		_	•	800	· ·	_						
Hct.	35.1	<del>-</del> .	Marri	_		-						
Medications		_		-	_	-						

AP: Antepartum; PP: post partum; S/D/M: systolic/diastolic/mean; HR: heart rate; PA: pulmonary artery; CO: cardiac output; CI: cardiac index; SVI: stroke volume index; PAR: pulmonary arteriolar resistance (indexed as HR units); TPR: total péripheral resistance (indexed as HR units); D₅W: 5% dextrose in water; D₅RL: 5% dextrose in Ringer's lactate; EBL: estimated blood loss; Hct.: hematocrit; IM: intramuscularly.

\*This patient presented at term with a BP of 180/120 mm Hg and a 17 pound weight gain in the week prior to admission. She was treated with a 4 gm loading dose of intravenous MgSO<sub>4</sub> and then started on a continuous infusion of 1 gm/hr. She was also given a single bolus injection of 5 mg of hydralaz:ne intravenously after which the BP ranged from 130 to 140/90 to 100 mm Hg. Labor was augmented with intravenous oxytocin, but 9 hours after admission and 6 hours after the initiation of the oxytocin infusion, she underwent a primary cesarean section for failure to progress. Because of significant oliguria vigorous hydration was undertaken during the AP period with the Swan-Ganz catheter in place. She received a total of 8,100 ml of D<sub>5</sub>/W and D<sub>5</sub>/RL along with 25 gm of SPA prior to delivery. Urine output during this period was 225 ml.

Table III. Measured and derived variables in Patient M. C.\*

	$Tim\epsilon$								
Variable	1 1/2 hr AP	1 hr AP	½ hr AP	Intubation	Delivery	1 hr PP			
BP (S/D/M)	190/110/137	180/103/132	190/90/123	200/100/133	160/90/113	180/80/113			
HR	110	93	100	111	78	87			
PA (S/D/M)	27/14/18	22/11/15	16/5/9	20/6/11	32/15/20	16/6/9			
PCWP '	3	ń	. 1	2	6	2			
CO	_	10.4	8.6	12.4	9.1	7.4			
CI	_	5.7	4.7	6.8	5.0	4.1			
SVI		58.9	47.7	62.0	64.8	47.2			
LVSWI	_	101	83.8	110.5	103.1	84.1			
PAR	-	1.5	1.6	1.3	2.7	1.7			
TPR		22.8	27.2	19.3	24.3	32.3			
Fluids:									
D <sub>5</sub> /W and D <sub>5</sub> /RL (ml)	600	575	300	300	_	625			
SPA (gm)	_	_	_		_	_			
Urine output (ml)	40	20	20	100	_	100			
EBL (ml)		; <del>-</del> ;	_	600	_				
Hct.	_	. —	38.7	-	-	<del>-</del>			
Medications		Hydralazine, 5 mg IV	Hydralazine, 5 mg IV	<del>-</del> .	-	Phenobarbital 60 mg IV and 60 mg IM			

For abbreviations see footnote to Table II. IV: Intravenously.

\*This patient presented to an outlying hospital with an initial BP of 220/140 mm Hg. She was treated with a 4 gm loading dose of intravenous MgSO<sub>4</sub> and started on a continuous infusion of 1 gm/hr. She was also given 10 mg of hydralazine intravenously and then transferred to YNHH. Admission BP was 190/110 mm Hg and three intermittent intravenous bolus injections of 5 mg of hydralazine were given during the AP course to maintain BPs in the range of 180 to 190/100 to 110 mm Hg. Intravenous oxytocin was administered but discontinued after 4 hours because of late feta, heart rate decelerations in association with hyperstimulation at 4 mU/min. The patient underwent primary cesarean section 6 hours following admission for failure to progress. She received total of 2,025 ml of D<sub>5</sub>/RL and D<sub>5</sub>/W and had a urinary output of 330 ml in the hospital prior to delivery.

من			·	Time				
	2 hr PP	3 hr PP	4 hr PP	5 hr PP	6 hr PP	7 hr PP	, 8 hr PP	9 hr PP
	172/90/117	152/80/104	156/90/112	150/90/110	170/90/117	_	160/90/113	140/80/100
	110	104	108	110	1 10	· <del></del>	108	102
	25/12/16	24/11/16	30/10/17	32/15/21	32/18/23	-	29/12/18	23/14/17
	14	14	20	20	22 -		17	16
	_	14.2	15.2	14.8	15.3	_	15.3	_
	_	6.4	6.9	6.7	6.9	_	6.9	<del></del>
		62.0	63.9	61.1	63.2	_	64.3	
		84.4	80.0	74.8	81.6	_	84.0	_
	-	0.46	0.14	0.14	0.28	′ –	0.28	-
	-	17.6	16.2	16.3	16.8	_	16.2	-
~-	-			• •				
	500	350	275	175	100	100	150	100
		25	<u>-</u>		1	_		'
	120	60	120	150	150	145	90	_
	-		- '	_	<del>-</del>	-	***	_
	34.8		_	-	·	-	29.9	_
	-	-	Phenobarbital,	_	Morphine,	· -	-	_
		· · · · · · · · · · · · · · · · · · ·	150 mg IM	•	10 mg IM	,		

	•						
2 hr PP	3 hr PP	4 hr PP	5 hr PP	6 hr PP	7 hr PP	8 hr PP	9 hr PP
<u>-</u>	180/90/120	180/86/117	190/94/126	190/80/117	200/60/106	210/60/110	220/85/13
_	92	84	80	93	98	88	97
_	21/9/13	23/12/16	25/17/20	30/18/22	30/18/22	29/19/22	33/20/24
_	8	12	15	20	18	20	20
_	9.4	10.5	11.4	10.4	14.3	12.7	12.4
_	5.2	5.8	6.3	5.7	7.9	7.0	6.8
_	56.7	69.4	79.1	62.1	81.0	80.0	71.0
_	86.4	99.1	108.7	76.0	97.0	98.1	106.2
_	0.95	0.68	0.78	0.34	0.50	0.28	0.58
_	22.9	20.0	. 18.3	19.0	, 13.3	15.5	18.8
						•	
450	150	510	325	275	175	200	175
· - ·		25	_	. =			·····
100	75	50	15		30	45	45
~=	-	-	_	` ' ·	<u> </u>	·	
-			32.3	<u> </u>	_		
-	Morphine, 15 mg IM	_	. <del>-</del> .	<b>-</b> ,	, _	,	

Table IV. Measured and derived variables in Patient B. J.\*

,	,	,	Time	•	
Variable `	1 hr AP	½ hr AP	Intubation	Delivery	1 hr PP
BP (S/D/M)	186/124/145	170/90/117	160/90/113	162/90/114	116/80/92
HR	112	116	116	110	105
PA (S/D/M)	_		28/16/20	28/14/19	18/2/9
PCWP	_	*****	14	14	4
	· <u>-</u>	-	8.3	7.8	6.7
CI	-		6.4	6.0	5.1
SVI	_	* ***	53.4	54.9	49.4
LVSWI	<u>—</u> ,	***	74.6	74.7	59.9
PAR	· _	New	0.93	0.66	0.57
TPR ·	_		17.5	18.8	17.7 -
	4	•	~		*
Fluids:					
$D_5W$ and $D_5RL$ (ml)	700	500	150		350
SPA (gm)		NAME .	_	manage."	_
Urine output (ml)		20	60	-	60
EBL (ml)	-	more a	600	e.ce	. –
Hct.	35	Monte	-	NA.	-
Medications	Hydralazine, 15 mg IV	and the second s	_	<u></u>	· -

For abbreviations see footnotes to Tables II and III.

\*This patient had three seizures at home and one on admission to the hospital. Fifty minutes after stabilization with an intravenous loading dose of 4 gm of MgSO<sub>4</sub> followed by a continuous infusion and 15 mg of hydralazine administered as an intravenous bolus a primary cesarean section was performed. A Swan-Ganz catheter was inserted in the operating room immediately prior to the operation. The data within the box represent the high-output state referred to within the text.

Therefore, our hemodynamic findings indirectly support Chesley's assertion.

Some investigators have stated that the decrease in blood volume observed in PET has no hemodynamic relevance.<sup>3</sup> We believe that this conclusion requires qualification. The assumption that the associated reduction in left ventricular filling pressure is invariably slight may not be valid. Vasodilating agents, an integral part of the management of acutely ill toxemic patients, can be expected to produce some venous dilatation. Epidural anesthesia may further compound this problem. Circulatory reflexes cannot be expected to compensate totally for abrupt changes of major magnitude in patients who are already hypovolemic.

Based on these observations we believe that if low indices of ventricular filling pressure are present in severe toxemia they should be corrected along with the other therapeutic measures being taken. A further reduction of cardiac preload secondary to an absolute or relative intravascular volume loss may result in hemodynamic decompensation.

Delivery period. Dramatic increases were noted in systemic and pulmonary blood pressures as well as PCWP values and cardiac indices during delivery. This was undoubtedly due in part to extrusion of blood from the uteroplacental bed into the central circulation, resulting in increased cardiac preload. The rapid induction-

intubation sequence associated with the light general anesthesia used in these patients may have compounded the situation.<sup>13</sup> Each hemodynamic profile required approximately 3 minutes to perform. Accordingly, within the time limits imposed by intubation and delivery, it was not possible to distinguish conclusively between intubation, cesarean section delivery, and delivery of the placenta.

Postpartum period. Ross and Braunwald<sup>7</sup> have shown that left ventricular function is normal when LVSWI increases in proportion to elevations of left ventricular end-diastolic pressure.<sup>7</sup> It is, therefore, important to know the LVSWI when interpreting the hemodynamic significance of an increase in PCWP. When this relationship was examined in our patients, no impairment of left ventricular contractility was detected (Fig. 1). This was true despite the potentially depressant effect of concurrently administered magnesium sulfate.

All three of the patients in this study received intravenous hydralazine. The cardiovascular effects of this agent include decreased vascular resistance and increased heart rate, stroke volume, and cardiac index. <sup>14</sup> While hydralazine may have contributed to the excellent ventricular function observed, it is unlikely to have played a major role because of the inconstancy of its administration and the small doses employed.

During the postpartum period one patient (B. J.) re-

Tene								
2 hr PP	3 hr PP	4 hr PP	5 hr PP	6 hr PP	7 hr PP	8 hr PP	9 hr PP	
130/80/97		163/90/114	180/108/132	183/109/134	160/90/113	154/90/111	116/90/99	
108		. 118	123	122	113	112	105	
18/4/7	· -	30/9/16	_	34/16/22	35/18/24	38/13/21	18/2/7	
6	, <del></del>	15	20	21	23	20	4	
6.6	· <del></del>	8.8		8.9	8.8	9.0	6.7	
5.1	_	6.8	_ ,	6.8	6.8	6.9	5.1	
47.3	-	57.8	_	56.5	60.5	62.2	50.9	
57.9		77.8		86.9	73.8	77.9	69.9	
0.19		0.14	-	0.14	0.14	0.28	0.57	
17.3	<del>-</del>	15.6	; <del>-</del>	18.4	15.5	15.1	18.8	
				•				
200	125	125	125	125	. 125	100	100	
		<del>-</del>	<del>-</del> ,	٠ –	′,* <u> </u>	-		
80	50	. 70	85	60	65	30	350	
		-	<u> </u>	<u>-</u>	No.			
31		_	_	-	-		***	
	*****	-	<u>-</u>	<u> </u>	Hydralazine, 20 mg IV	Furosemide, 20 mg IV		

ceived diuretic therapy because of elevated indices of left heart filling pressure despite fluid restriction. Therapy was directed toward a high-output state characterized by hypertension, elevated cardiac and left ventricular stroke work indices, and PCWPs in excess of 20 mm Hg (Table II). The high-output state demonstrated by this patient might be responsible for many cases of postpartum hypertension which are relatively refractory to the usual doses of vasodilators. The elevated indices of left ventricular filling pressure may reflect an increase in circulating blood volume caused by resorption of edema fluid or iztrogenic overload secondary to fluid administration significantly in excess of urinary excretion. The other elevated values probably represent the response to hypervolemia of a heart with excellent mechanical function.  $^{7, 15}$  When this entity exists in the postpartum period the administration of a diuretic should facilitate concurrent vasodilator therapy. The high-output state we have observed may be analogous to that described by Davidson and Parry<sup>16</sup> in a group of normal Nigerian women where fluid retention caused by a high salt intake was associated with postpartum pulmonary edema.

#### Conclusion

The patients studied in this series were receiving drug and fluid therapy while the data were being collected. Our results, therefore, do not necessarily provide insight into the natural history of severe PET at the time of delivery and must be interpreted with this in mind.

Three severely toxemic patients have been demon-

Table V. Formulas for derived data

$$BSA (sq m) = Ht. (cm^{0.725} \times weight (kg)^{0.425} \times 71.84 \times 10^{-4}$$

$$CI (L/min/sq m) = \frac{CO}{BSA}$$

$$SVI (ml/beat/sq m) = \frac{CI}{HR}$$

$$PAR (mm Hg min^{-1} sq m) = \frac{(MPAP - \overline{PCWP})}{CI}$$

$$(indexed as HR units)$$

$$TRP (mm Hg min L^{-1} sq m) = \frac{(BP(M) - \overline{PCWP})}{CI}$$

$$(indexed as HR units)$$

$$LVSWI (gm m/sq m) = SVI \times (BP(M) - \overline{PCWP}) \times 0.0136$$

For abbreviations see footnote to Table II. MPAP: Mean pulmonary artery pressure.

strated to have higher LVSWIs than healthy, nonpregnant patients. In addition, the pulmonary vasculature did not seem to be involved in a primary vasospastic process. Finally, at least in terms of central intravascular pressures, the antepartum period was associated with a decrease in circulating blood volume. At delivery, an increase in PCWP and cardiac index occurred primarily because of an increase in venous return. The postpartum period differed from the antepartum period in that it was associated with an increased PCWP, which seems to reflect an increase in circulating blood volume rather than a pathologic diminution of cardiac reserve.

These findings suggest that, coincident with the administration of vasodilators, intravenous fluid therapy should be aggressive during the antepartum period. Diuretic therapy during this period should be specifically reserved for those instances where central fluid overload has been demonstrated. Following delivery, however, the rate of fluid administration should be reduced and diuretics may be a useful therapeutic adjunct in patients with a high-output state.

#### REFERENCES

- Assali, N. S., Holm, L. W., and Parker, H. R.: Systemic and regional alterations in toxemia, Circulation (Suppl. 2) 29,30:11, 1964.
- Chesley, L. C.: Plasma and red cell volumes during pregnancy, Am. J. Obstet. Gynecol. 112:440, 1972.
- 3. Assali, N. S., and Vaughn, D. L.: Blood volume in preeclampsia: Fantasy and reality, Am. J. Obstet. Gynecol. 129:355, 1977.
- Goodlin, R. C., Cotton, D. B., and Haesslein, H. C.: Severe edema-proteinuria-hypertension gestosis, Am. J. OBSTET. GYNECOL. 132:595, 1978.
- Holmgren, A., Johnsson, B., and Sjostrand, T.: Circulatory data in normal subjects at rest and during exercise in recumbent position, with special reference to the stroke volume at different work intensities, Acta Physiol. Scand. 49:343, 1960.
- Parmley, W., Tomoda, H., Diamond, G., Forrester, S., and Crexells, C.: Dissociation between indices of pump performance and contractility in patients with coronary artery disease and acute myocardial infarction, Chest 67:141, 1975.
- Ross, J., Jr., and Braunwald, E.: The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotensin, Circulation 29:739, 1964.
- 8. Barrett-Boyes, B. G., and Wood, E. H.: Cardiac output and related measurements and pressure values in the

- right heart and associated vessels, together with an analysis of the hemodynamic response to the inhalation of high oxygen mixtures in healthy subjects, J. Lab. Clin. Med. 51:72, 1958.
- 9. Snell, R., and Luchsinger, P. C.: Determination of external work and power of the left ventricle in intact man, Am. Heart J. 69:529, 1965.
- 10. Ueland, K., and Hansen, J. M.: Maternal cardiovascular dynamics: Labor and delivery under local and caudal anesthesia, Am. J. Obstet. Gynecol. 103:8, 1969.
- 11. Swan, H. J. C.: The role of hemodynamic monitoring in the management of the critically ill, Crit. Care Med. 3:83, 1975.
- 12. Chesley, L. C.: Hypertensive Disorders in Pregnancy, New York, 1978, Appleton-Century-Crofts, p. 203.
- 13. Prvs-Roberts, L. T., Meloche, G. R., and Foex, P.: Studies of anesthesia in relation to hypertension. II. Haemodynamic consequences of induction and endotracheal intubation, Br. J. Anaesth. 43:531, 1971.
- Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 5, New York, 1975, Macmillan Publishing Co., Inc., pp. 705-706.
   Sarnoff, S. J., and Berglund, E.: Starling's Law of the
- Sarnoff, S. J., and Berglund, E.: Starling's Law of the heart studied by means of simultaneous right and left ventricular function curves in the dog, Circulation 9:706, 1954.
- Davidson, N. McD., and Parry, E. H. O.: Postpartum fluid retention, Q. J. Med. 47:431, 1978.

# Stable prolactin level after enhanced estradiol production following dehydroepiandrosterone sulfate

A. KAUPPILA, M.D.
O. YLIKORKALA, M.D.

Oulu, Finland

To evaluate whether intravenous injection of dehydroepiandrosterone sulfate (DHEAS), by enhancing estradiol ( $E_2$ ) production, would stimulate prolactin (PRL) secretion in late pregnancy, maternal serum PRL was determined before and 1 to 5 hours after administration of 100 mg of DHEAS in a total of 41 women with normal or complicated late pregnancies (twin pregnancy, pre-eclampsia, intrahepatic cholestasis of pregnancy, diabetes). The basal serum PRL concentration in patients with diabetes was significantly lower than normal. The mean PRL level did not change significantly in any group in spite of the increase in serum  $\Xi_2$  levels after the DHEAS injection. The lack of PRL response to a rapid rise in  $E_2$  may be due to the maximal inhibition of the PRL-inhibiting factor in the hypothalamus and/or maximal activation of the pituitary lactotrophs occasioned by the high estrogen environment during late pregnancy. (AM. J. OBSTET. GYNECOL. 138:271, 1980.)

THE TENFOLD to twentyfold increase in serum prolactin (PRL) during pregnancy is generally attributed to the parallel rise in estrogens, 1-4 which prevents the release of PRL-inhibiting factor (PIF) in the hypothalamus<sup>5</sup> and/or directly promotes pituitary synthesis of PRL.<sup>6</sup> It has not been known so far whether additional estrogen stimulation would result in enhanced PRL release during late human pregnancy. An increased placental synthesis of estradiol (E2) can be caused by the administration of dehydroepiandrosterone sulfate (DHEAS).7 The serum E2 level has been reported to increase about twofold to fivefold within 1 hour after an intravenous injection of 50 to 100 mg of DHEAS.8-10 Therefore, the aim of the present work was to determine whether the pituitary lactotrophs are capable during late pregnancy of responding to an E2 rise with increased PRL secretion.

#### Patients and methods

Forty-one patients between the thirtieth and fortieth gestational week were studied (Table I). Eight women had normal pregnancies, and there were complications of pregnancy in 33 cases. The patients were thoroughly informed about the purpose of the study, and they all had given their consent.

From the Departments of Obstetrics and Gynecology and Clinical Chemistry, University of Oulu.

Received for publication November 9, 1979.

Revised May 2, 1980.

Accepted May 29, 1980.

Reprint requests: Dr. Antti Kauppila, Department of Obstetrics and Gynecology, University of Oulu, SF-90220 Oulu 22, Finland.

The test was started at 0800 with an intravenous infusion of isotonic saline. The first blood sample was drawn 30 minutes later and a bolus of 100 mg of DHEAS (Hoffmann-La Roche, Basel, Switzerland) was then injected intravenously. Thereafter, blood samples were taken hourly for 5 hours. The patients were in the lateral or oblique lateral recumbent position throughout the study. Serum was stored at  $-20^{\circ}$  C until assayed for  $E_2^{11}$  and PRL<sup>12</sup> by radioimmunoassay. Serial determinations for a given patient were always run in the same batch of the assay. Intra-assay variation was 5% to 7% and interassay variation was 10% to 12% (N = 20). The paired t test and Student's t test were employed in the statistical analysis of the results.

#### Results

The initial mean serum PRL level in patients with diabetes was significantly lower (p < 0.01) than the corresponding value in women with normal pregnancy.

Although the mean serum  $E_2$  level rose significantly (p < 0.01) in every group the mean PRL level did not change in any group of patients within 5 hours of the start of DHEAS injection (Table I).

#### Comment

We had previously measured E<sub>2</sub> levels in the same serum samples in which we determined PRL.<sup>10</sup> The mean E<sub>2</sub> level rose significantly I hour after DHEAS injection in patients with normal or complicated pregnancies. However, the mean PRL level in the same women did not change. It is likely that the high basal concentration of E<sub>2</sub> had already stimulated pituitary PRL secretion and/or blocked the release of hypothalamic PIF as much as possible, and thus an addi-

**Table I.** Prolactin and estradiol-17 $\beta$  values (mean  $\pm$  SEM) before and after DHEAS injection in normal and complicated pregnancies

	Prolactin ( µg/L)								Estradiol-17β (nmoles/L)	
. •	Gestational	Before DHEAS	Hours after DHEAS					n. C		
Type of pregnancy			1	2	3	4	5	Before DHEAS	1 hour after DHEAS	
Normal (n = 8) Twin (n = 10)	$37.1 \pm 1.2$ $34.8 \pm 0.6$	203 ± 32 206 ± 26	165 ± 25 198 ± 30	180 ± 87 194 ± 30	188 ± 33 197 ± 30	193 ± 37 187 ± 21	197 ± 35 189 ± 19	62 ± 11 92 ± 14	270 ± 50 452 ± 69	
Pre-eclampsia $(n = 9)$	$36.1 \pm 0.9$	$196 \pm 33$	$157 \pm 23$	$164 \pm 19$	$178\pm29$	$192 \pm 25$	$173 \pm 23$	$58 \pm 10$	$217 \pm 35$	
Intrahepatic cholestasis $(n = 7)$	$36.3 \pm 0.5$	$187 \pm 36$	$153 \pm 17$	$166 \pm 31$	162 ± 14	$131 \pm 32$	$171 \pm 26$	$75 \pm 14$	$412 \pm 61$	
Diabetes $(n = 7)$	$35.4 \pm 0.5$	$108 \pm 9$	$101 \pm 6$	$98 \pm 7$	$108 \pm 6$	$121 \pm 21$	$91 \pm 14$	$86 \pm 10$	$289 \pm 40$	

tional rise in E<sub>2</sub> failed to elicit any further PRL rise. The PRL level in late pregnancy also remained unaffected by E<sub>2</sub> depression due to the maternal dexamethasone treatment, as reported previously. These findings suggest that in late pregnancy the pituitary PRL secretion cannot be affected by changing the serum level of E<sub>2</sub>. One may argue that the study period of 5 hours was too short for any PRL change to appear. This seems unlikely since in the presence of lower estrogen concentrations in midgestation an intravenous injection of 100 mg of DHEAS was associated with significantly elevated PRL levels in maternal serum after 2 hours. However, the pituitary response of increased PRL secretion is not totally blunted by high estrogen

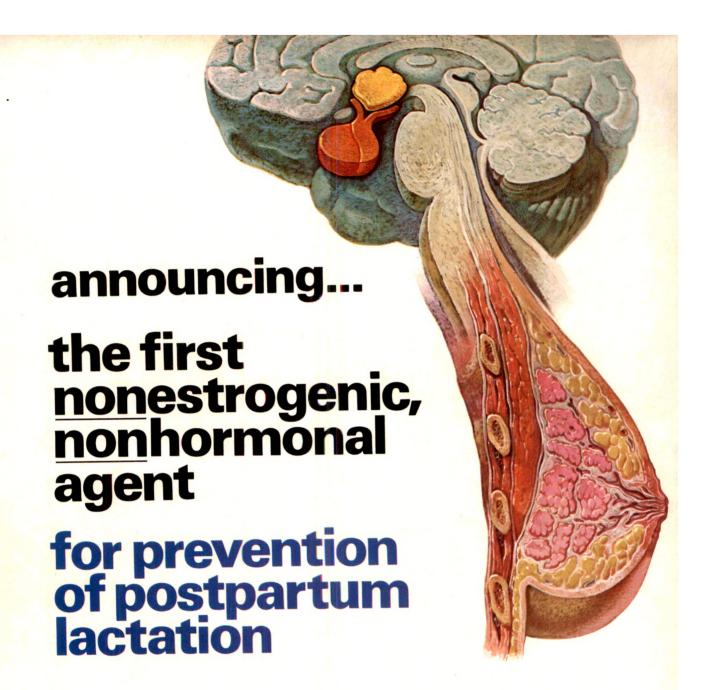
concentrations, since the administration of thyrotropin-releasing hormone, which directly stimulates pituitary lactotrophs, also leads to a significant PRL rise in serum during late pregnancy.<sup>4</sup>

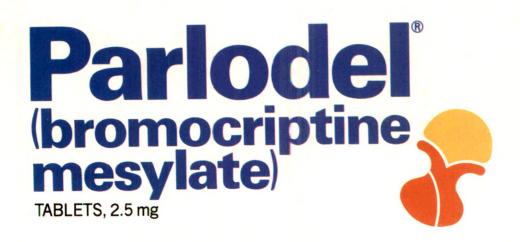
It was previously reported that in pregnant diabetic patients the serum PRL level is at times lower than normal. <sup>15,16</sup> This was also confirmed in our study. It is well known that the offspring of diabetic mothers have an increased risk of respiratory distress syndrome. Because PRL may be involved in the regulation of fetal pulmonary maturation, <sup>17</sup> it remains to be ascertained whether the low PRL level in the serum of the diabetic mother is responsible for the delayed pulmonary maturation in the fetus.

#### REFERENCES

- Hwang, P., Guyda, H., and Friesen, H. G.: A radioimmunoassay for human prolactin, Proc. Natl. Acad. Sci. USA 68:1902, 1971.
- Tyson, J. E., Hwang, P., and Guyda, H.: Studies of prolactin secretion in human pregnancy, Am. J. Obstet. Gynecol. 113:14, 1972.
- 3. Aubert, M. L., Grumbach, M. M., and Kaplan, S. L.: Heterologous radioimmunoassay for plasma human prolactin (hPRL); values in normal subjects, puberty, pregnancy and pituitary disorders, Acta Endocrinol. (Kbh.) 77:460, 1974.
- 4. Ylikorkala, O., Kivinen, S., and Reinilä, M.: Serial prolactin and thyrotropin responses to thyrotropin releasing hormone throughout normal human pregnancy, J. Clin. Endrocrinol. Metab. 48:288, 1979.
- Meites, J., and Clemens, J. A.: Hypothalamic control of prolactin secretion, Vitam. Horm. 30:165, 1972.
- 6. Jacobi, J., Lloyd, H. M., and Meares, J. D.: Onset of estrogen-induced prolactin secretion and DNA synthesis by the rat pituitary gland, J. Endocrinol. 72:35, 1977.
- Lauritzen, C.: Conversion of DHEAS to estrogens as a test of placental function. A clinical test for placental activity using DHEA sulphate and ACTH injections in pregnant women, Acta Endocrinol. (Suppl.) 119:188, 1967.
- Fraser, I. S., Leask, R., Drife, J., Bacon, L., and Michie, E.: Plasma estrogen response to dehydroepiandrosterone sulphate injection in normal and complicated late pregnancy, Obstet. Gynecol. 47:152, 1976.
- Klopper, A., Varela-Torres, R., and Jandial, V.: Placental metabolism of dehydroepiandrosterone in normal pregnancy, Br. J. Obstet. Gynaecol. 83:478, 1976.

- Ylöstalo, P., Kauppila, A., Reinilä, M., Tuimala, R., and Ylikorkala, O.: Conversion of dehydroepiandrosterone sulphate to estrogens in intrahepatic cholestasis and other complications of pregnancy, Clin. Endocrinol. (Oxf.) 12:121, 1980.
- 11. Hammond, G. L., Viinikka, L., and Vihko, R.: Automation of radioimmunoassay for some sex steroids with use of both iodinated and tritiated ligands, Clin. Chem. 23:1250, 1977.
- Hammond, G. L., Kontturi, M., Määttälä, P., Puukka, M., and Vihko, R.: Serum FSH, LH and prolactin in normal males and patients with prostatic diseases, Clin. Endocrinol. (Oxf.) 7:129, 1977.
- Kauppila, A., Puukka, M., and Tuimala, R.: Effect of dexamethasone on prolactin secretion in late pregnancy, Am. J. Obstet. Gynecol. 134:752, 1979.
- Ylikorkala, O., Kauppila, A., and Viinikka, L.: Intraamniotic or intravenous injection of dehydroepiandrosterone sulphate in midgestation: Effect on prolactin level in maternal serum and amniotic fluid, J. Clin. Endocrinol. Metab. 49:452, 1979.
- Kivinen, S., Ylikorkala, O., and Puukka, M.: Prolactin response to thyrotropin-releasing hormone in normal and complicated late pregnancies, Obstet. Gynecol. 54:695, 1979.
- Sadovsky, E., Weinstein, D., Ben-David, M., and Polishuk, W. Z.: Serum prolactin in normal and pathological pregnancy, Obstet. Gynecol. 50:559, 1977.
- Hauth, J. C., Parker, C. R., MacDonald, P. C., Porter, J. C., and Johnston, J. M.: A role of fetal prolactin in lung maturation, Obstet. Gynecol. 51:81, 1978.



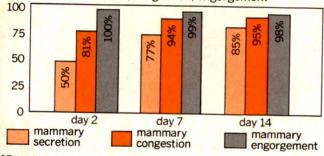


# The need for an alternative to estrogens and other hormones in the prevention of postpartum lactation is met with Parlodel (bromocriptine mesylate)

# Extremely high clinical response, based on complete absence—not just relief—of mammary secretion, congestion, and engorgement

By day 14 of Parlodel therapy,\* 85% of the patients who completed at least 14 days of therapy had complete absence of secretion, and all but two of these women achieved this response by day 12; in the remaining 15%, secretion was rated as slight to moderate. By day 7, 94% of the patients had complete absence of congestion, and this remained essentially unchanged through day 14. Furthermore, 98% had complete absence of engorgement; significantly, few patients developed engorgement at any time during therapy—never over 9%.

Percent of patients reporting complete absence of mammary secretion, congestion, engorgement\*



\*Based on 70 patients who completed at least 7 days of therapy and 66 patients who completed at least 14 days of therapy. Half of each group received 5.0 mg a day and the other half received 7.5 mg a day, in divided doses.

It should be kept in mind that the incidence of significant painful engorgement is low and usually responsive to appropriate supportive therapy. In contrast with supportive therapy, Parlodel (bromocriptine mesylate) prevents the secretion of prolactin, thus inhibiting lactogenesis and subsequent secretion, congestion, and engorgement.

In other studies <sup>1,2</sup> with Parlodel therapy it was noted that there "were no complaints of engorged or painful breasts..." and that "... the almost complete relief of pain and engorgement spared both the patient and the nursing staff many complaints, and justified the longer duration of treatment."

Mild to moderate secretion, congestion, or engorgement occurs in 18% to 40% of patients once therapy is stopped.

## High correlation between clinical response and reduction of prolactin levels demonstrated<sup>3</sup>

In nine postpartum patients Parlodel therapy was initiated after delivery. Five hours after the first Parlodel dose, serum prolactin levels had fallen to the normal range and, over the eight days they were measured, remained below an estimated mean normal. Prolactin concentrations did not rise even following nipple stimulation in the five patients tested in this manner. None of the nine patients had any milk secretion or breast engorgement.

#### No effect on clotting factors 4,5

Adverse reactions were generally mild to moderate and required discontinuation of therapy in only 3% of 234 patients treated with 2.5 mg to 7.5 mg daily for prevention of postpartum lactation. Headache, dizziness, nausea, and hypotension were among the side effects observed. (See Brief Summary.)

### Recommended dosage and administration in prevention of postpartum lactation

 one 2.5-mg tablet bid with meals for 14 days (if necessary, may be given for up to 21 days); since Parlodel (bromocriptine mesylate) is known to cause hypotension in some patients, therapy should be started only after vital signs have been stabilized and no sooner than four hours after delivery

1. Rolland R, De Jong FH, Schellekens LA, Lequin RM: The role of prolactin in the restoration of ovarian function during the early post-partum period in the human female: II. A study during inhibition of lactation by bromergocryptine. *Clin Endocrinol* 4:27-38, 1975. 2. Rolland R, Schellekens L: A new approach to the inhibition of puerperal lactation. *Br J Obstel Gynaecol* 80:945-951, 1973. 3. Brun del Re R, del Pozo E, de Grandi P, et al: Prolactin inhibition and suppression of puerperal lactation by a Br-ergocryptine (CB 154): A comparison with strogen. *Obstel Gynecol* 41:884-990, 1973. 4. Nilsen PA, Meling AB. Abildgaard U: Study of the suppression of lactation and the influence or blood clotting with bromocriptine (CB 154) (Parlodel\*): A double blind comparison with diethylstilboestrol. *Acta Obstel Gynecol Scand* 55:39-44, 1976. 5. Cooke 1, Foley M. Lenton E, et al: The treatment of puerperal lactation wit bromocriptine. *Postgrad Med J* 52(suppl 1):75-80, 1976.

Indications: Short-term treatment of amenorrhea/galactorrhea associated with hyperprolactinemia due to varied etiologies, excluding demonstrable pituitary tumors; not indicated in patients with normal prolactin levels, and, since safe use has not been demonstrated in pregnancy, not indicated in management of infertility.

Prevention of physiological lactation, (secretion, congestion, and engorgement) after parturition, when the mother elects not to breast feed or breast feeding is contraindicated, or after stillbirth or abortion. The physician should keep in mind that the incidence of significant painful engorgement is low and usually responsive to appropriate supportive therapy. In contrast with supportive therapy, Parlodel® (bromocriptine mesylate) prevents the secretion of prolactin, thus inhibiting lactogenesis and subsequent

secretion, congestion, and engorgement. Once Parlodel therapy is stopped, 18% to 40% of patients experience rebound of breast secretion, congestion, or engorgement, which is usually mild to moderate in severity.

Contraindications: Sensitivity to any ergot alkaloids.

Warnings: Since hyperprolactinemia with amenorrhea/galactorrhea has been found in patients with pituitary tumors (Forbes-Albright syndrome), a complete evaluation of the sella turcica is advisable before treatment with Parlodel (bromocriptine mesylate). Although Parlodel therapy will effectively lower plasma levels of prolactin in patients with pituitary tumors—this does not obviate the necessity of radiotherapy or surgical procedures where appropriate. If pregnancy occurs, treatment should be discontinued immediately.

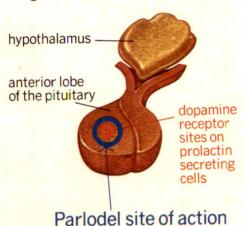
In postpartum studies, hypotension (decrease in supine systolic and diastolic pressures of greater than 20 mm and 10 mm Hg respectively) has been observed in almost 30% of patients; on occasion, supine systolic pressure dropped as much as 50 to 59 mm Hg. It is likely that many of these hypotensive episodes were not drug induced, since decreases in blood pressure are frequently noted during the puerperium independent of drug therapy. Since Parlodel (bromocriptine mesylate) is known to cause hypotension in some patients, however, Parlodel therapy should not be initiated until the vital signs have been stabilized and no sooner than four hours after delivery. Periodic monitoring of the blood pressure, particularly during he first few days of therapy, is advisable and care should be exercised during concomiant administration with other medications known to lower blood pressure. Since dizziness (8% to 16%) and syncope (less than 1%) have been reported, patients should be cautioned about engaging in activities requiring rapid and precise responses, such as driving an automobile or operating dangerous machinery.

**Precautions:** Since treatment of amenorrhea/galactorrhea may result in restoration of fertility, patients should be required to use contraceptive measures, other than the oral contraceptives, during treatment; however, since patients often ignore this recommenda-

© 1980 Sandoz, Inc.

# The action of Parlodel® (bromocriptine mesylate) compared with that of hormones in the prevention of postpartum lactation

With the shedding of the placenta following birth, estrogen and progesterone levels fall dramatically. Consequently, the lactogenic effects of elevated prolactin on the mammary gland are no longer blocked by these steroids.



Parlodel (bromocriptine mesylate), as a dopamine receptor agonist, reduces prolactin levels by acting directly on dopamine receptor sites on prolactin secreting cells in the anterior pituitary. With the rapid decline of prolactin levels, the stimulus leading to and supporting lactation is removed, and congestion and engorgement are prevented. Parlodel (bromocriptine mesylate) is not known to act directly on mammary tissue.



#### Hormonal site of action

Estrogens, which actually stimulate prolactin secretion, are thought to inhibit the binding of prolactin to its receptors in the mammary glandular cells responsible for milk secretion. Estrogens prevent lactation by blocking the lactogenic effects of prolactin in a manner similar to the effects of estrogen during pregnancy. Since prolactin levels remain elevated, congestion and engorgement are possible.

the first nonestrogenic, nonhormonal agent for the prevention of postpartum lactation

# 2.5 mg bid with meals for 14 days (if necessary, may be continued for an additional 7 days) bromocriptine mes



tion and since pregnancy may occur prior to reinitiation of menses, as an additional precaution, a pregnancy test is recommended at least every four weeks during the amenorrheic period and, once menses are reinitiated, every time a patient misses a menstrual period. Parlodel therapy has been demonstrated to be effective in the short-term management of amenorrhea (galactorine) data are not available on the order. ment of amenorrhea/galactorrhea; data are not available on the safety or effectiveness of its use in long-term continuous dosage or in patients given repeated courses of treatment following recurrence of amenorrhea/galactorrhea after initial treatment. Recurrence rates are reportedly very high, ranging from 70% to 80% in domestic and foreign studies.

Decreases in blood pressure are common during the puerperium and, since Parlodel therapy produces hypotension in some patients, the drug should not be administered until the vital signs have been stabilized, and care should be exercised when it is administered concomitantly with other medications known to lower blood pressure. Safety and efficacy have not been established in patients with renal or hepatic disease. Diuretics

and phenothiazines should be avoided during Parlodel therapy.

Nursing Mothers: Since it prevents lactation, the drug should not be administered to

mothers who elect to breast feed their offspring.

Pediatric Use: Safety and efficacy have not been established in children under the age of 15.

Use in Pregnancy: Safe use has not been established.

Adverse Reactions: The incidence of adverse effects is quite high (68%) in patients treated for amenorrhea/galactorrhea, but only 23% of patients treated within the recommended dosage range for prevention of physiological lactation had at least one side effect. Adverse reactions were generally mild to moderate and required discontinuation of therapy in only 6% of patients treated for amenorrhea/galactorrhea and 3% of patients treated for amenorrhea/galactorrhea and 3% of patients treated for prevention of physiological lactation. A hypotensive effect, usually transient, may accompany treatment; two reports of fainting in the puerperium may possibly be related to this effect. The occurrence of adverse reactions may be lessened by temporarily reducing dosage to one-half tablet two to three times daily.

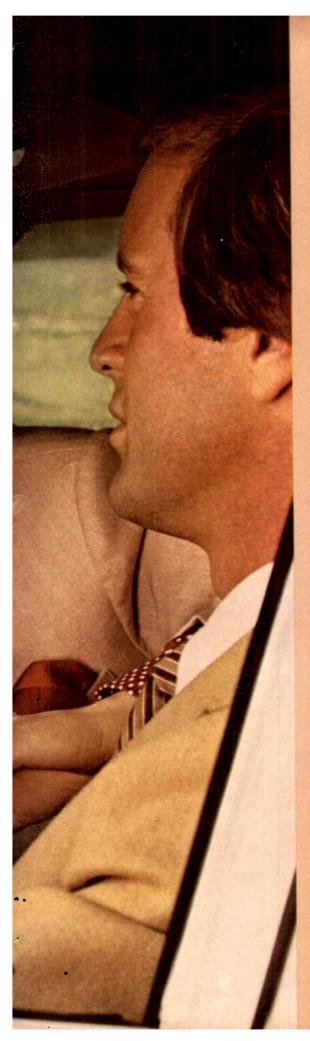
The following table shows the most frequent adverse reactions.

Treatment of Amenorrhea/ Galactorrhea	Adverse Reaction	Prevention of Lactation
51%	Nausea	7%
18%	Headache	10%
16%	Dizziness	8%
8%	Fatique	1%
7%	Abdominal Cramps	0.4%
6%	Lightheadedness	_
5%	Vomiting	3%
5%	Nasal Congestion	_
3%	Constipation	_
3%	Diarrhea	0.4%
570	Syncope	0.7%
	Hypotension	28%
	I- smanarhan /anlantarrhan	the thereneu

Dosage and Administration: In amenorrhea/galactorrhea, the therapeutic dosage is one 2.5-mg tablet, two or three times daily with meals, and duration of treatment not to exceed six months; it is recommended that treatment commence with one tablet daily, increasing to a therapeutic dosage within the first week, to reduce the possibility of adverse reactions. In prevention of physiological lactation, therapy should be started only after the patient's vital signs have been stabilized and no sooner than four hours after delivery; the recommended therapeutic dosage is one 2.5-mg tablet twice daily with meals; the usual dosage range is from one 2.5-mg tablet daily to one 2.5-mg tablet thre times daily with meals; therapy should be continued for 14 days, however, may be given for up to 21 days if necessary. **How Supplied:** Tablets, 2½ mg, in packages of 30.

Before prescribing or administering, see package circular for full product information.





# LOESTRIN 1.5/30

(1.5 mg norethindrone acetate and 30 mcg ethinyl estradiol tablets, USP)

...He says there's no sense taking more estrogen than you need."

LOESTRIN\*1.5/30 limits estrogen exposure and often reduces the frequency of estrogen-related side effects, because it contains just 30 mcg of ethinyl estradiol. LOESTRIN 1.5/30 combines this low estrogen dose with norethindrone acetate, a progestin that's been used alone for years in gynecologic therapy. Together, they offer more than 99% effective oral contraception.

When you're considering starting new patients on the "pill" or switching patients from higher estrogen-containing OCs to the low-dose ones, consider LOESTRIN 1.5/30...available in a 21-day regimen and the convenient 28-day regimen which includes 7 days of iron tablets to take during the "off-week" and simplifies remembering to take the medication.

LOESTRIN 1.5/30...highly effective protection with limited estrogen exposure

Please see following page for prescribing information.

PARKE-DAVIS

Div of Warner-Lambert Co Morris Plains, NJ 07950 USA

Brief Summary of Prescribing Information
LOESTRIN® 1.5/30
(1.5 mg norethindrone acetate and 30 mcg ethinyl estradiol tablets, USP) See section under Special Notes on Administration and How Supplied.

DESCRIPTION

Loestrin 1.5/30 Products are progestogen-estrogen combinations. INDICATION AND USAGE

INDICATION AND USAGE
Loestrin 1.5/30 Products are indicated for the prevention of pregnancy in women who elect to
use oral contraceptives.
In clinical trials with Loestrin 1.5/30 involving 17,139 therapy cycles, there was a pregnancy
rate of 0.49 per 100 woman years.

Dose-related risk of thromboembolism from oral contraceptives: Studies have shown a
positive association between the dose of estrogens in oral contraceptives and the risk of
thromboembolism. It is prudent and in keeping with good principles of therapeutics to minimize
exposure to estrogen. The oral contraceptive prescribed for any given patient should be that
product which contains the least amount of estrogen that is compatible with an acceptable
pregnancy rate and patient acceptance.

CONTRAINDICATIONS

#### CONTRAINDICATIONS

ONTRAINDICATIONS

1. Thrombophlebitis or thromboembolic disorders

2. A past history of deep-vein thrombophlebitis or thromboembolic disorders

3. Cerebral vascular or coronary artery disease

4. Known or suspected carcinoma of the breast

5. Known or suspected estrogen-dependent neoplasia

6. Undiagnosed abnormal genital bleeding

7. Known or suspected pregnancy (See No. 5 under WARNINGS.)

ARNINGS

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke. The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

should be familiar with the following information relating to these risks.

1. Thromboembolic Disorders and Other Vascular Problems: An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is wellestablished. Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic.

Cerebrovascular disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater who accordate with oral contraceptives has been reported confirming a previously suspected association. These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor.

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about a tivice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who do not smoke, but about a tenfold to twelvefold increased risk of training and the risk of thrombotic amount of smoking is also an important factor.

Since of deep the an analysis of data. Ruise hyperstrators concluded that the risk of thrombotic amount of smoking is also an important factor.

amount of smoking is also an important factor.

Risk of dose: In an analysis of data, British investigators concluded that the risk of throm boembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives; however, the quantity of estrogen may not be the sole factor involved.

Estimate of excess mortality from circulatory diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers.

rette smokers.

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke.

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders. Should any occur or be suspected, the drug should be discontinued immediately.

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

2. Ocular lesions: Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contraceptive if there

2. Ocular lesions: Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions.

3. Carcinoma: Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver.

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported. However, there is no evidence suggestion in creased risk of endometrial carcinoma contractions.

evidence suggesting increased risk of endometrial cancer in users of conventional combina

evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives.
Studies found no evidence of increase in breast cancer in women taking oral contraceptives; however, an excess risk in users with documented benign breast disease was reported. There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of users is, nevertheless, essential. In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care.

who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care.

4. Hepatic Tumors: Benigh hepatic adenomas have been found to be associated with oral contraceptives. Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. Usage in or Immediately Preceding Pregnancy: Birth Defects in Offspring, and Malignancy in Female Offspring: During early pregnancy, female sex hormones may seriously damage the offspring.

Female Offspring: During early pregnancy, remained and the defects and limb defects, has offspring. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives. Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrial periods. If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuals of the pregnancy should be discussed.

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

Administration of progressogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. Gallbladder Disease: Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives.

7. Carbohydrate and Lipid Metabolic Effects: Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed.

8. Elevated Blood Pressure: An increase in blood pressure has been reported in patients receiving oral contraceptives. The prevalence in users increases with longer exposure. Age is also strongly correlated with development of hypertension. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure.

9. Headache: Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives.

10. Bleeding Irregularities: Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, nonfunctional causes should be borne in mind. In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or mallignancy.

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives.

11. Ectopic Pregnancy: Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

failures.

12. Breast Feeding: Oral contraceptives may interfere with lactation. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers eiving these drugs.

PRECAUTIONS

1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.

2. Preexisting uterine leiomyomata may increase in size.
3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.
4. Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated.

only with careful monitoring, in patients with conditions which might be aggravated.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice. If jaundice develops, the medication should be discontinued.

6. Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function.

7. Users may have disturbances in normal tryptophan metabolism, which may result in a relative psylidoxine deficiency.

8. Serum folate levels may be depressed.

9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted.

are submitted.

10. Certain endocrine and liver function tests and blood components may be affected.

(a) Increased sulfobromophthalien retention. (b) Increased prothrombin and factors VII, VIII, IX, and X: decreased antithrombin 3: increased norpinephrine-induced platelet aggregability. (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone. (d) Decreased pregnanediol excretion. (e) Reduced response to metyrapone test.

Drug interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of infampin and an association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and ampicillin.

**ADVERSE REACTIONS** 

An increased risk of the following serious adverse reactions has been associated with oral

contraceptives.

Thrombophlebitis; Pulmonary embolism; Coronary thrombosis; Cerebral thrombosis; Cerebral hemorrhage; Hypertension; Gallbladder disease; Benign hepatomas; Congenital

anomalies.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed. Mesenteric thrombosis, Neuro-ocular lesions, eg. retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: gastrointestinal symptoms; breakthrough bleeding, spotting; change in menstrual flow; dysmenor-rhea; amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema; chloasma or melasma; breast changes; change in weight; change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately post partum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidasis; change in corneal curvature; intolerance to contact lenses.

The following adverse reactions have been reported and the association has been neither

The following adverse reactions have been reported and the association has been neither

confirmed nor refuted.

Premenstrual-like syndrome; cataracts; changes in libido; chorea, changes in appetite; cystitis-like syndrome; headache, nervousness; dizziness; hirsutism; loss of scalp hair; ythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis, porphyria

Special Notes on Administration

Loestrin [21] 1.5/30 (1.5 mg norethindrone acetate and 30 mcg ethinyl estradiol tablets.

USP) — Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication.

fifth day, after discontinuing medication.

Loestrin Fe 15/30—Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after the brown ferrous fumarate tablets have been started. Because of the relatively low estrogenic content, Loestrin 15/30 is not a good cyclic regulator. There are patients whose inherent hormone balance will require larger amounts of estrogen than that contained in Loestrin 15/30 to achieve cyclic regularity. These patients experience altered bleeding patterns, which do not conform to treatment schedules.

The physician should be alert to the fact that the irregular bleeding patterns could mask bleeding from organic cause, and appropriate diagnostic measures should be taken if the bleeding persists or continues after changing to a higher estrogen-content product. After several months, bleeding may be reduced to a virtual absence, reduced flow may be a result of medication and not indicative of pregnancy.

HOW SUPPLIED

HOW SUPPLIED

Loestin [Eg 1.5/30 is available in compacts each containing 21 green tablets and 7 brown rablets. Each green tablet contains 1.5 mg of norethindrone acetate and 30 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate. Available in packages of five

compacts and packages of five refills.

Loestrin [21] 1.5/30 is available in compacts each containing 21 tablets. Each green tablet contains 1.5 mg of norethindrone accetate and 30 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

#### **PARKE-DAVIS**

### FETUS, PLACENTA, AND NEWBORN

Morphologic and histochemical evidence for the occurrence of collagenolysis and for the role of neutrophilic polymorphonuclear leukocytes during cervical dilation

L. C. U. JUNQUEIRA

M. ZUGAIB

G. S. MONTES

O. M. S. TOLEDO

R. M. KRISZTÁN

K. M. SHIGIHARA

São Paulo, Brazil

Biopsy specimens of nonpregnant and intrapartum human cervices were studied by electron microscopy, and by the Picrosirius-polarization method which is a specific procedure for the detection of collagen fibers in tissue sections. The results obtained demonstrate a marked reduction of collagen fibers in the intrapartum material as compared to the samples of nonpregnant cervices. Evidence that indicated the presence of a widespread collagenolysis in the intrapartum biopsy specimens was obtained by both optical and electron microscopy, thus suggesting that this might be the main cause of the changes in the cervix that permit it to dilate during parturition. The study of the neutrophilic polymorphonuclear leukocytes in the intrapartum biopsy specimens strongly suggested that these cells participate in this process. (Am. J. OBSTET. GYNECOL. 138:273, 1980.)

SINCE demonstration that the uterine cervix is constituted predominantly of collagen fibers, 1, 2 it has become evident that dilation of the cervix should be explained by changes in the components of its connective tissue.3

From the Laboratories for Cell Biology, Rheumatology, and Obstetric Physiology, Medical School, University of São Paulo.

Supported by Grants 79/47 and 79/704 from the Fundação de Amparo à Pesquisa do Estado de São Paulo.

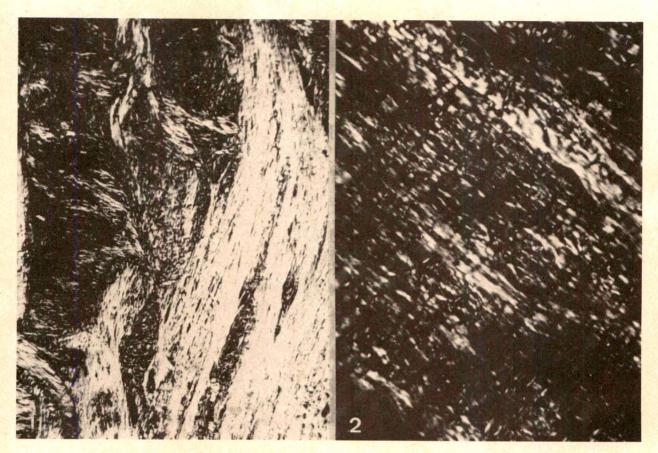
Received for publication April 23, 1980.

Accepted April 30, 1980.

Reprint requests: L. C. U. Junqueira, Faculdade de Medicina, Biologia Celular, Av. Dr. Arnaldo 455, 01246 São Paulo, Brazi<mark>l</mark>. On the basis of study of human<sup>4</sup> and rat<sup>3</sup> cervices, the suggestion was made that softening of the cervix might be due to an increase in its polysaccharide and water content that promotes a longitudinal division of the collagen fibers into their subunits.

Further observations in human material, based mainly on the quantitation of collagen from dilated cervices that measured their hydroxyproline content, 5, 6 showed a moderate reduction in the amount of collagen, thus suggesting that this fact might be related to the phenomenon. Recently, however, the reduction of collagen content could not be confirmed, 7 but evidence for the occurrence of collagen depolymerization during cervical dilation has been presented. 6, 7

Despite these contributions, attention has been called



Figs. 1 and 2. Photomicrographs of sections of nonpregnant (1) and intrapartum (2) human cervices. Picrosirius-polarization method by which collagen fibers appear as bright birefringent structures against a dark background. Observe that in the nonpregnant cervix the collagen appears as bundles of continuous, densely packed fibers. In the apparently empty region in the upper left portion, the collagen bundles are not birefringent because of their orientation parallel to the direction of the polarized light. In the intrapartum cervices, the aspect is quite different; the collagen fibers appear separated and irregularly fragmented, and the amount of collagen fibers per area is drastically reduced. (Fig. 1, ×100. Fig. 2, ×375.)

in a recent review<sup>8</sup> to the fact that the discrepancy between the relatively moderate biochemical variations of the cervix and the dramatic changes in its morphologic and physical properties which allow expulsion of the fetus still remains to be explained.

On the basis of a specific method described in this laboratory for the histochemical detection of collagen, 9, 10 and on the study of the human cervix by electron microscopy, we present evidence in this report to indicate that collagen depolymerization is a widespread phenomenon during cervical dilation.

Furthermore, the study of the distribution and alterations presented by the neutrophilic polymorphonuclear leukocytes in our material strongly suggests that these cells, which are known as a source of collagenase, <sup>11–13</sup> may have an important role in this process.

The time-honored expression "cervical dilation" will be used in this report to indicate, as well, the changes that induce the softening of this structure and actually permit its dilation during parturition.

#### Methods

Our material derives from 16 biopsy specimens of cervical tissue of normal patients, obtained during parturition, and 10 biopsy specimens from nonpregnant, sexually active women. These specimens were cut in half, with one part being used for optical and electron microscope studies, and the other part, for chemical assay.

**Optical microscopy.** The biopsy specimens were fixed in Bouin's fluid for 24 hours, dehydrated, and embedded in paraffin. Five-micrometer sections were stained with hematoxylin and eosin, and also by the Picrosirius method. When the Picrosirius-stained slides are observed by polarization microscopy, the method is specific for oriented polymerized collagen molecules.

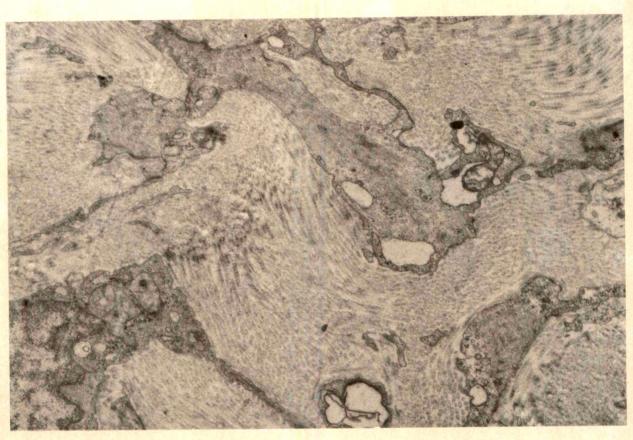


Fig. 3. Electron micrograph of a biopsy specimen from a nonpregnant cervix. Observe the close packing of the collagen fibrils forming collagen fibers. Between the collagen, segments of fibroblasts.  $(\times 16, 100.)$ 

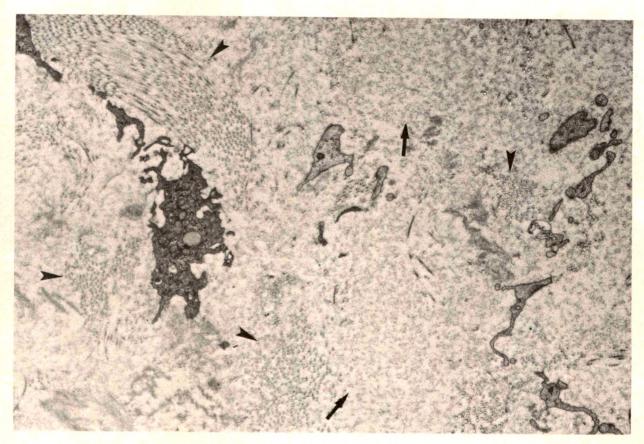
(collagen fibers), in the sense that only these structures present a bright yellow or red birefringence.9 However, the method does not detect depolymerized collagen whose molecules are not oriented as fibers. Because depolymerized collagen lacks orientation, it is not birefringent, even though it stains red with the dye used.

Electron microscopy. Small fragments of cervix were fixed in 2% glutaraldehyde dissolved in 0.15M phosphate buffer at pH 7.2, followed by postfixation in 1% osmium tetroxide for 1 hour, and overnight block staining in 0.5% aqueous uranyl acetate. The tissues were embedded in a polyester resin (Polilyte), thin sectioned in an LKB ultratome, double-stained by uranyl acetate and lead citrate, and studied with a Zeiss EM 9 S electron microscope.

Morphometry. The diameter of cross-sectioned collagen fibrils was measured with a Bausch and Lomb measuring magnifier in electron micrographs enlarged to a convenient size. A minimum of 100 measurements of fibril diameters was made in each biopsy specimen. The magnification of the electron microscope was calibrated with a diffraction grating.

Quantitation of collagen fibrous material by microspectrophotometry associated with the Picrosirius-polarization method. On the basis of the fact that oriented collagen molecules (collagen fibrils and fibers) increase considerably in birefringency after reacting with the dye Sirius Red, and that this method is specific for oriented collagen molecules,9 measurements of the intensity of birefringency were performed in Picrosirius-stained sections of specimens from nonpregnant and intrapartum cervices. Polarization was obtained with two Polaroid filters located one below the condenser and another above the objective lens. Light intensity was measured with a Reichert model 6 A E 9/65 microspectrophotometer, with a 585 nm wavelength. A low-power (2.6×) Zeiss aplanatic objective was used in these measurements. The light intensity of 20 random fields from one section of each specimen was measured. Optical conditions were regulated so that the light intensity of sections from nonpregnant cervices gave an average value of around 50% transmittance in the microamperimeter.

Glycosaminoglycan identification and quantitation. The isolation of glycosaminoglycans in nonpregnant



**Fig. 4.** Biopsy specimen from an intrapartum cervix. Great reduction in the amount of collagen fibrils (*arrowheads*) and the appearance of a diffuse granular deposit (*arrows*) that occupies most of the area normally filled by collagen fibrils in the biopsy specimens from nonpregnant cervices. (×9,900.)

and intrapartum biopsy specimens was performed by subjecting homogenates of the samples to proteolytic digestion, alkaline hydrolysis, and alcoholic precipitation, as described.<sup>14</sup>

Identification and quantitation of the glycosaminoglycans were performed by means of degradation by specific mucopolysaccharidases and microelectrophoresis in agarose gel.<sup>15</sup>

#### Results

Connective tissue stroma. The study of Picrosirius-stained sections of nonpregnant and intrapartum cervices by optical microscopy disclosed various features. The nonpregnant cervices were comprised almost exclusively of dense connective tissue formed by thick collagen fibers that were stained dark red. In the intrapartum material, the collagen fibers appeared to be much thinner and more spread out. This aspect was, however, quite irregular; thus, a few zones with more or less compact collagen were observed, surrounded by many regions with a low density of collagen. Between the regions containing collagen fibers, an amorphous

material could be seen which stained less intensely with Sirius Red.

A careful analysis of the collagen fibers showed that they did not dissociate into thinner components, but that, in most regions, irregularities, expressed by lack of continuity, variable thickness, etc., suggested that they were being corroded. This picture was seen in greater detail when studied by the Picrosirius-polarization method, which specifically showed the collagen fibers as strongly birefringent yellow structures against a dark background. Since with this method the morphologic features of the fibers from intrapartum biopsy specimens could be observed more clearly, the results obtained strongly reinforced the idea that there was a local degradation of the collagen fibers (Figs. 1 and 2). With polarization microscopy, the amorphous deposits of red-stained material described above could not be seen because they were not birefringent.

These observations with the optical microscope were supported by the study of this material with the electron microscope, as is clearly shown in Figs. 3 and 4. Observe that in the nonpregnant cervix there were regularly

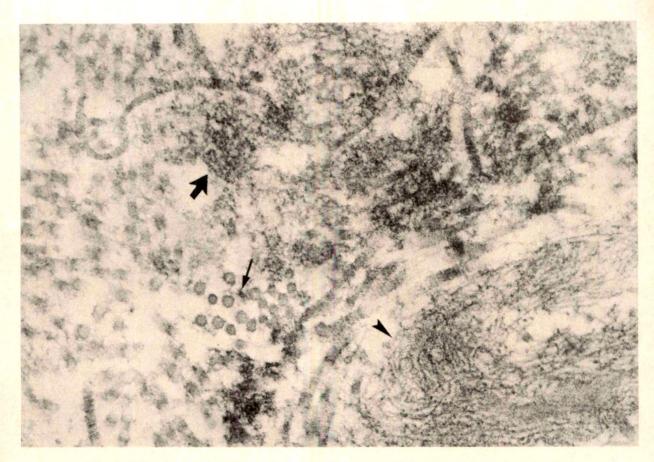


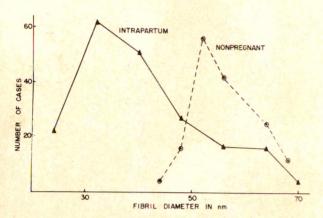
Fig. 5. High magnification of a section from an intrapartum biopsy specimen showing a typical region with morphologic aspects that suggest collagenolysis. Observe the fuzzy aspect of the collagen fibrils and the appearance of transversely sectioned fibrils with variable diameters (thin arrow). Note the presence of microfibrils (arrowhead) and areas occupied by granular material, in some parts of which there are aspects suggestive of the transition of microfibrils to granules (thick arrow). ( $\times$ 65,200.)

compact, and clearly visible, bundles of collagen fibrils which formed collagen fibers. In the intrapartum cervices, this regular arrangement was disturbed: the collagen fibrils were not oriented in an orderly fashion, they were irregularly separated from one another, and images that suggested their corrosion and resolution into aggregates of microfibrils were present (Fig. 5). Furthermore abundant deposits of microfibrillar or granular material, that probably corresponded to the apparently amorphous material described with optical microscopy, frequently appeared between the fibrils. Transitional aspects between the microfibrils and the granular material could be clearly seen (Fig. 5).

The fact that, with few exceptions, Picrosirius stained specifically collagenous material,9 in association with the above-mentioned morphologic aspects, strongly suggested that this granular material was probably the result of the agglomeration of partially depolymerized collagen. However, these structures, despite their staining red with Picrosirius, were not birefringent, a characteristic that one might have expected in collagenous material whose molecules were not oriented in a fibrillar manner.

The study of the diameter of the collagen fibrils from our material showed that the fibrils from nonpregnant cervices had a regular diameter, whose average (56.6 ± 5.5) coincided with our observations on the collagen fibers from other regions of the human body. 16, 17 On the other hand, the intrapartum cervices had irregular fibrils with smaller and more variable diameters, with an average of 42.1 ± 11.3. The foregoing morphometric findings are illustrated in Fig. 6. These results expressed quantitatively the above-mentioned corroded aspect of the collagen fibrils, and confirmed the hypothesis that this aspect was due to collagenolysis.

The study of the cell population in biopsy specimens of nonpregnant cervices showed that fibroblasts were



**Fig. 6.** Histogram showing the frequency of collagen fibril diameters in intrapartum and nonpregnant human cervical biopsy specimens. The fibrils from the intrapartum specimens show not only a smaller average diameter but also a distinctly higher variation in their values when compared to the fibrils from nonpregnant specimens.

**Table I.** Comparative birefringency intensity (measured as % transmission) in seven specimens from nonpregnant and intrapartum human cervices, with use of the Picrosirius-polarization method in association with microspectrophotometry

Nonpregnant	Intrapartum
38.0	3.5
40.3	6.6
42.5	7.3
49.1	1.4
31.8	1.4
65.1	2.8
56.4	4.0
verage 46.2	3.8

the main constituent. In the intrapartum material the cellular population increased, with the appearance of mast cells and macrophages in addition to the fibroblasts. The most common cell, however, was the neutrophilic polymorphonuclear leukocyte, which heavily infiltrated the stroma. The characteristics of this massive tissue invasion by neutrophils will be described further on.

Quantitation of collagen fibrous material by microspectrophotometry in association with the Picrosirius-polarization method. The results obtained are presented in Table I. Observe that the light intensity emitted by the birefringency of Picrosirius-stained collagen fibers was considerably less in the intrapartum than in the nonpregnant material. Thus, if the average transmittance observed in the nonpregnant specimens was considered as 100%, the intrapartum material had an average transmittance of 8.3%. This speaks strongly



Fig. 7. Photomicrograph of an intrapartum specimen showing an intense passage of neutrophilic polymorphonuclear leukocytes across a venule (V) into the surrounding tissue.  $(\times 340.)$ 

in favor of a massive decrease in oriented collagen molecules associated with cervical dilation. These findings agree with the intense reduction in birefringent collagen fibers observed in histologic sections analyzed by the Picrosirius-polarization method and illustrated in Figs. 1 and 2.

Chemical study of glycosaminoglycans. The results obtained are summarized in Table II, which shows that no great changes in the type and content of glycosaminoglycans occurred relative to cervical dilation.

The small relative increase in chondroitin sulfates 4 and 6, and the moderate reduction in the dermatan sulfate contrast with the dramatic histologic and histochemical changes observed and suggest that they are of relatively little importance in this process.

Neutrophilic polymorphonuclear leukocytes. The study of our material in the optical and electron microscopes revealed a series of characteristics in regard to the appearance and distribution of neutrophilic polymorphonuclear leukocytes. In contrast to the findings in specimens from nonpregnant cervices, these cells appeared in great quantity in all of the specimens from intrapartum cervices. They were especially visible in



Fig. 8. Electron micrograph from an intrapartum biopsy specimen comparing an intravascular (right) with an extravascular (left) neutrophil. Observe the drastic reduction of the specific granules in the extravascular leukocyte. The arrowhead shows the capillary wall. (×8,850.)

Table II. Sulfated glycosaminoglycans composition of nonpregnant and intrapartum human cervices

	Total sulfated	Sulfated glycosaminoglycans (%)				
Cervix	glycosaminoglycans (mg/gram of dry tissue)	Chondroitin 4/6-sulfates	Dermatan sulfate	Heparitin sulfate		
Nonpregnant			81.5	16.4		
1	2.23	<5	80.0	17.5		
2	2.48	<5		20.0		
3	1.95	<5	77.0			
Mean	2.22	<5	79.5	17.9		
Intrapartum			00	22		
1	2.63	15	63			
9	3.48	16	63	21		
3	2.50	17	69	14		
Mean	2.87	16	65	19		

the inner surface of the venules and frequently could be seen crossing their walls and migrating between the collagen fibers of the surrounding tissue (Fig. 7).

Once in the tissue, these cells had a tendency to lose their specific granules, which appeared less numerous when compared to leukocytes in intravascular location (Fig. 8). Isolated nuclei, with the morphologic characteristics of neutrophil nuclei, were frequently found, thus suggesting that this degranulation process was followed by the dissolution of these cells' cytoplasm, and, consequently, cell death. In many cases a positive relationship between the amount of infiltrated cells and the degree of collagenolysis could be observed.

Another suggestive aspect, seen by both optical and electron microscopy, was the appearance of a halo surrounding these intratissular neutrophils. Examination with the electron microscope revealed that this halo was due to the disappearance of collagen fibrils around these cells.

No infiltration of neutrophils could be observed in any of the specimens from nonpregnant cervices.

We think that the above-mentioned characteristics strongly suggest an active participation of these cells in the process of cervical dilation.

Preliminary observations performed in biopsy specimens obtained during pregnancy suggest that the processes of collagenolysis and infiltration of neutrophils occur throughout pregnancy but are accelerated prior to, and during, labor.

#### Comment

Our observations strongly suggest that an active collagenolysis occurs in order to prepare the cervix for parturition. Thus not only do the collagen fibers appear dissociated in this process, but there is also optical and electron microscopic evidence of the lysis of these structures. Furthermore, the hypothesis of a lytic process was reinforced by our morphometric findings.

The fact that the association of the Picrosirius-polarization method with microspectrophotometry shows a marked reduction in the quantity of collagen fibers in the intrapartum material, when compared to nonpregnant samples, confirms by means of a more refined method the above-mentioned observations. It is interesting to observe that the decrease in collagen fibers, as measured by the above-mentioned method, is much more intense than the results presented in the literature measuring the amount of collagen in nonpregnant and intrapartum human cervices by means of its hydroxyproline content.5-7 This discrepancy might be explained by the presence of the agglomerated Sirius Red-stained material present in the areas of intense collagenolysis. This material might consist of partially depolymerized collagen, as suggested by the fact that, although it stained with Sirius Red, no birefringency was observed by polarization microscopy. As such, it would preserve its high hydroxyproline content but lose its characteristic birefringency because of the loss of the molecular orientation originally present in its collagen fibrils. This material might also be responsible for the increase in collagen solubility observed in intrapartum cervices.6, 7

The above-mentioned considerations lead us to believe that the evidence presented here argues strongly in favor of the existence of an extensive collagenolytic process during cervical dilation, which agrees with findings reported in the literature.<sup>5–7</sup> Biochemical assays for collagenase activity in biopsy specimens of nonpregnant and intrapartum cervices would be of interest to check this hypothesis.

Our observations with regard to the intense infiltration of neutrophils in the intrapartum cervices coincide with the findings reported in the literature. This process is so conspicuous that the pathologists have described a typical cervicitis present during pregnancy. 18–20 Analysis of the characteristics of this neutrophilic invasion strongly suggests that these cells may play an important role in the process of cervical dilation. The fact that neutrophils are a well-studied source of collagenase 11–13 reinforces this idea.

Since these observations suggest that the infiltration of neutrophils into the intrapartum cervix is a physiologic phenomenon, the designation of cervicitis for this process may have to be reconsidered.

Since no characteristic changes could be shown in the glycosaminoglycans of the intrapartum cervices, as compared to nonpregnant cervices, our findings do not support the suggestions<sup>3, 4</sup> that these substances play a leading role in the process of cervical dilation.

Summing up, we think that our findings point to collagenolysis as being the main process which allows cervical dilation by promoting tissue softening. The deposition of partially lysed collagen in the extracellular space probably explains the discrepancy observed between the modest changes in hydroxyproline content and the dramatic histologic and functional modifications observed during cervical dilation.

#### Addendum

Since the submission of this manuscript, two papers that strongly support our hypothesis have been published. Thus, three forms of collagenase were detected in the human cervix (Kitamura, K., Ito, A., and Mori, Y.: The existing forms of collagenase in the human uterine cervix, J. Biochem. 87:753, 1980), and cervical collagenase activity has been found to be higher at parturition than in nonpregnant cervices (Mochizuki, M., and Tojo, S.: Effect of dehydroepiandrosterone sulfate on softening and dilatation of the uterine cervix in pregnant women, *in* Naftolin, F., and Stubblefield, P. G., editors: Dilatation of the Uterine Cervix, New York, 1980, Raven Press, p. 267).

#### REFERENCES

- Danforth, D. N.: The fibrous nature of the human cervix, and its relation to the isthmic segment in gravid and nongravid uteri, Am. J. Obstet. Gynecol. 53:541, 1947.
- 2. Danforth, D. N.: The distribution and functional activity of the cervical musculature, Am. J. Obstet. Gynecol. 68:1261, 1954.

- Bryant, W. M., Greenwell, J. E., and Weeks, P. M.: Alterations in collagen organization during dilatation of the cervix uteri, Surg. Gynecol. Obstet. 126:27, 1968.
- Danforth, D. N., Buckingham, J. C., and Roddick, J. W.: Connective tissue changes incident to cervical effacement, Am. J. Obstet. Gynecol. 89:939, 1960.
- Danforth, D. N., Veis, A., Breen, M., Weinstein, H. G., Buckingham, J. C., and Manalo, P.: The effect of pregnancy and labor on the human cervix: Changes in collagen, glycoproteins and glycosaminoglycans, Am. J. Ob-STET. GYNECOL. 120:641, 1974.
- Kleissl, H. P., Van der Rest, M., Naftolin, F., Glorieux, F. H., and Leon, A. D.: Collagen changes in human cervix at parturition, Am. J. Obstet. Gynecol. 130:748, 1978.
- Maillot v., K., and Zimmermann, B. K.: The solubility of collagen of the uterine cervix during pregnancy and labour, Arch. Gynecol. 220:275, 1976.
- Stys, S. J.: Changes in the cervix at parturition, in Friedman, E. A., Noah, M. L., and Work, B. A., Jr., editors: Uterine physiology, Proceedings of a Brook Lodge Workshop, Littleton, Massachusetts, 1979, PSG Publishing Co., p. 53.
- Junqueira, L. C. U., Bignolas, G., and Brentani, R. R.: Picrosirius staining plus polarization microscopy, a specific method for collagen detection in tissue sections, Histochem. J. 11:447, 1979.
- tochem. J. 11:447, 1979.

  10. Junqueira, L. C. U., Cossermelli, W., and Brentani, R. R.: Differential staining of collagens type I, II and III by Sirius Red and polarization microscopy, Arch. Histol. Jpn. 41:267, 1978.
- Lazarus, G. S., Daniels, J. R., Brown, R. S., Bladen, H. A., and Fullmer, H. M.: Degradation of collagen by a human granulocyte collagenolytic system, J. Clin. Invest. 47: 2622, 1968.

- 12. Ohlsson, K., and Olsson, I.: The neutral proteases of human granulocytes: Isolation and partial characterization of two granulocyte collagenases, Eur. J. Biochem. **36:**473, 1973.
- Horwitz, A. L., Hance, A. J., and Crystal, R. G.: Granulocyte collagenase: Selective digestion of type I relative to type III collagen, Proc. Natl. Acad. Sci. U.S.A. 74:897, 1977
- Mourão, P. A. S., Rozenfeld, S., Laredo, J., and Dietrich,
   C. P.: The distribution of chondroitin sulfates in articular
   and growth cartilages of human bones, Biochim. Biophys.
   Acta 428:19, 1976.
- Dietrich, C. P., and Dietrich, S. M. C.: Electrophoretic behaviour of acidic mucopolysaccharides in diamine buffers, Anal. Biochem. 70:645, 1976.
- 16. Junqueira, L. C. U., Montes, G. S., and Krisztán, R. M.: The collagen of the vertebrate peripheral nervous system, Cell Tissue Res. 202:453, 1979.
- Montes, G. S., Krisztán, R. M., Shigihara, K. M., Tokoro, R., Mourão, P. A. S., and Junqueira, L. C. U.: Histochemical and morphological characterization of reticular fibers, Histochemistry 65:131, 1980.
- Epperson, J. W. W., Hellman, L. M., Galvin, G. A., and Busby, T.: The morphological changes in the cervix during pregnancy, including intraepithelial carcinoma, Am. J. OBSTET. GYNECOL. 61:50, 1951.
- Johnson, L. D.: Dysplasia and carcinoma in situ in pregnancy, in Norris, H. J., Hertig, A. T., and Abell, M. R., editors: The Uterus, International Academy of Pathology Monographs, Baltimore, 1973, Williams & Wilkins, p. 382.
- 20. Blaustein, A. L.: Pathology of the female genital tract, Heidelberg, 1977, Springer Verlag, p. 120.

# Effects of maternal cigarette smoking on fetal breathing and fetal movements

I. THALER, M.D.
J. D. S. GOODMAN, M.B., M.R.C.O.G.
G. S. DAWES, D.M., F.R.C.O.G., F.R.S.
Oxford, England

The effect of cigarette smoking on fetal breathing and fetal movements was studied in 10 women with low-risk pregnancy of 34 to 38 weeks' gestation. A continuous Doppler ultrasound method was used to measure fetal breath intervals. Smoking two cigarettes caused a small increase in the rate of fetal breathing (p < 0.01), which persisted for 60 minutes; the proportion of time the fetus spent breathing was not changed. There was a decrease in the number of fetal movements felt by the mother. These findings are discussed in relation to the alleged pathophysiologic effects of tobacco smoking on the fetus. (Am. J. Obstet. Gynecol. 138:282, 1980.)

SINCE the first report on human fetal breathing in utero with the use of an ultrasound method,1 a large body of literature has appeared2 which concentrates on the incidence of breathing (i.e., the proportion of time that fetal breathing movements are present) rather than its pattern. Yet observations on sheep have shown that the pattern of breathing, whenever present, is of importance as a diagnostic index of fetal health.3 Recently, it has become possible to record fetal breath intervals quantitatively by means of the continuous Doppler ultrasound method. Therefore, we have taken the opportunity to study the effects of maternal cigarette smoking on fetal breath intervals and on fetal body movements and to reexamine the effect of smoking on the incidence of breathing in low-risk pregnancy.

The original reports on the effects of smoking on fetal breathing, with use of the A-scan ultrasound method to follow movements of the chest wall, described a reduction in the incidence of fetal breathing that lasted an hour or more. <sup>4, 5</sup> There are three reasons

From the Nuffield Institute for Medical Research, University of Oxford.

Supported by grants from the Medical Research Council, the Tobacco Advisory Council, and Action Research for the Crippled Child.

Received for publication September 12, 1979.

Revised March 19, 1980.

Accepted June 11, 1980.

Reprint requests: Dr. Israel Thaler, Department of Obstetrics and Gynecology, Rambam Medical Centre, Haifa, Israel. for treating this evidence with reserve. First, although injection or infusion of nicotine into the descending aorta of the pregnant ewe caused a decrease in fetal breathing accompanied by, and attributed to, hypoxemia, only doses of nicotine that were larger than those anticipated from human smoking were effective. Second, observations on human fetal breathing activity by real-time B-scan and/or by continuous Doppler ultrasound showed an incidence of breathing substantially less than that reported with the A-scan method. It seemed likely that the A-scan method recorded both breathing and body movements. And third, measurements in sheep showed that movements of the chest wall do not give a direct, reliable measure of fetal breathing.

The present study showed that cigarette smoking does not reduce the incidence of fetal breathing, but does alter the frequency distribution of breath intervals, the mean rate of breathing, and the number of fetal body movements recorded by the mother.

#### Material and methods

Ten women volunteered for the study. They ranged in age from 20 to 34 years, had uncomplicated pregnancies of 34 to 38 weeks' gestation, and smoked 8 to 25 cigarettes (of a middle tar yield) a day. Observations were made after the women had abstained from smoking for 12 hours or more, and after they had eaten a breakfast that contained at least 55 gm of carbohydrate and 345 calories (average, 80 and 482, respectively).

Measurements were started between 0930 and 1000 hours, 60 to 90 minutes after breakfast, with the

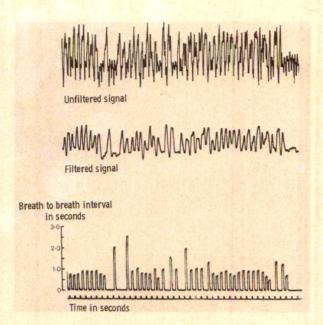


Fig. 1. Records of Doppler shift frequencies before and after filtering (above) from an ultrasound transducer on the maternal abdomen, showing the rise in frequency with increased velocity of fetal inferior vena caval blood flow on inspiration. The lowest record shows the breath interval derived instantaneously from a peak detector.

women in a semirecumbent position. Within the first 30 to 40 minutes (the control period), each woman was given a light snack, which supplied, on the average, 25 gm of carbohydrate and 250 calories.

Each woman was monitored on 2 successive days, at the same time of day and after the same breakfast. This procedure was adopted in order to minimize, insofar as possible, the effects of episodic variation in fetal breathing, possibly associated with changes in sleep state. On the first day, five women were asked to smoke two cigarettes of their own brand at the end of the control period; no cigarettes were given on the following day (Group A). The procedure was reversed for the other five women, so that they had no cigarettes on the first day, and two cigarettes on the following day (Group B). The women were randomly allocated to the two groups. Fetal breathing records were continued for 60 to 90 minutes after the control period; this constituted the study period. The mean duration for smoking the two cigarettes was 15.5 minutes. Each woman recorded the presence of fetal movements.

Fetal breathing was recorded by means of a continuous ultrasound Doppler instrument (Sonicaid D205 M) with a 2 MHz transducer, as described by Boyce and associates.8 The audible Doppler shift frequencies, due to the increased velocity of flow in the great veins below the heart on descent of the diaphragm,9 were recorded

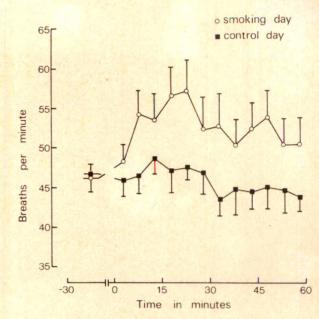


Fig. 2. Rate of fetal breathing (±SE) on the control day (■) and on the day when two cigarettes were smoked (beginning at zero time, o).

on a tape recorder (Sony TC 15350) and were later replayed into a peak frequency follower and analyzer.9 The intervals between successive peaks were displayed on a multichannel recorder (MX-4 Devices Instruments, England). Fig. 1 demonstrates the output signal from the peak frequency follower, together with the corresponding breath intervals measured to within 100 msec. Artifacts due to fetal or maternal movement were readily identified and were excluded.

Mean breathing intervals and the root mean square (RMS) values were calculated for each 5-minute epoch; only segments that contained at least 30 breaths were used for further analysis. The proportion of time the fetus spent breathing was also calculated for each 5-minute epoch. Statistical significance was determined by analysis of variance and paired t test, with each fetus serving as its own control.

#### Validation

Simultaneous visual real-time B-scan (Nuclear Enterprise Sector Scanner) and audible continuous Doppler ultrasound records of fetal breathing movements were made on a video-recorder. Over 5,000 breaths were identified by independent observers, with the use of visual signals and/or audible. Each observer pressed a key whenever he identified a breath, and the proportion of coincidences within 0.25 second was recorded. There was good agreement, but when both the audible signals were compared, the agreement was substantially better, 95% versus 92% for visual-visual and for

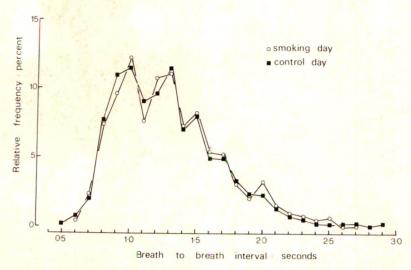


Fig. 3. Frequency distribution (%) of breath intervals on the control day (•) and during the control period of the day on which cigarettes were smoked (0).

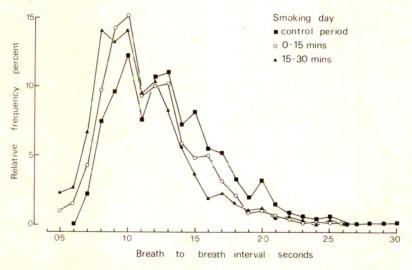


Fig. 4. Frequency distribution (%) of breath intervals before (•), during (0, 0 to 15 minutes), and after smoking two cigarettes (A, 15 to 30 minutes).

visual-audible comparisons. We concluded that it was easier to identify a fetal breath with certainty with the continuous Doppler method, which was also better repeatable than visualization of the chest wall with the real-time method.

#### Results

The effect of smoking two cigarettes on fetal breathing rate is shown in Fig. 2. The mean breathing rates in the control periods of both the smoking and the nonsmoking days were similar,  $46.2 \pm 1.8$  (SE) min<sup>-1</sup> and  $46.5 \pm 1.5 \text{ min}^{-1}$  respectively. The mean frequency distributions of breath intervals were almost identical during the control period of the two days (Fig. 3), and showed evidence of a bimodal distribution.

Within the first 5 minutes from the start of smoking, there was an increase in fetal breathing rate, which reached  $54.2 \pm 3 \text{ min}^{-1}$  at 10 minutes (Fig. 2) and rose to a peak of  $57.1 \pm 3.9 \text{ min}^{-1}$  between 20 and 25 minutes. There was a shift to the left in the frequency distribution of breath intervals, the peak of which became higher. The shift was maximal between 15 and 30 minutes (Fig. 4). Over the next 30 minutes the rate of fetal breathing declined. At 60 minutes it was still above the control level ( $50.4 \pm 3.3 \,\mathrm{min^{-1}}$ , Fig. 2), and the frequency distribution was still somewhat to the left of that in the control period. An analysis of variance was carried out on the mean breathing rates in the control period and in the following four 15-minute epochs of the study period, with the use of the data from all 10

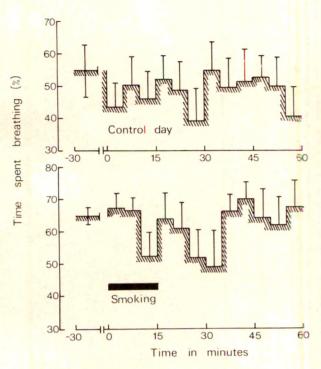


Fig. 5. Incidence (proportion of time  $\pm$  SE) of fetal breathing with (below) or without (above) smoking two cigarettes.

women. On the smoking day there were significant differences between the mean rates of breathing in the five epochs (p < 0.025). A paired t test between the mean rates of breathing in the control period and each of the following 15-minute epochs showed a significant increase in breathing rate in the first and second 15minute epochs after smoking started (p < 0.01).

The rate of breathing on the control day is shown in Fig. 2. Analysis of variance did not show a significant difference between the mean rates of breathing in the five epochs (p < 0.05). Table I shows the mean breath intervals for the control periods and the following two 30-minute epochs for each day.

The variability of breath intervals was determined as the RMS value of the differences from the mean. The RMS value for both the control periods was 397 msec. It declined slightly on both the smoking and nonsmoking days during the study period, to an average of 358 msec.

In order to determine whether the variability was related to the rate of breathing, regression analysis between breath intervals and RMS values in 5-minute epochs was performed. A highly significant correlation was found between the two (r = 0.45, p < 0.001), thereby showing that variability increased as breaths slowed. This relationship held both before and after smoking. However, the regression lines obtained from all the 5-minute epochs on the control day and in the

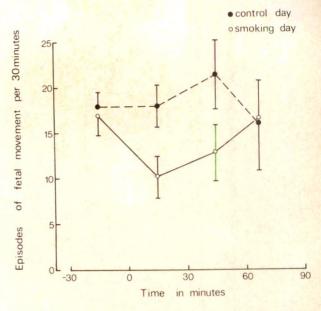


Fig. 6. Numbers of fetal movements (per 30 minutes, ±SE) recorded by the mothers with (o) or without (•) smoking two cigarettes.

Table I. Mean values ± SE of breath intervals (sec) in 10 human fetuses in the absence and presence of maternal smoking

	No smoking	Maternal smoking		
Control period	$1.29 \pm 0.006 (4,375)$	$1.30 \pm 0.006 (5,205)$		
0-30 min	$1.27 \pm 0.005 (4,227)$	$1.13 \pm 0.005 (5,676)^*$		
0-60 min	$1.39 \pm 0.006 (3,492)$	$1.18 \pm 0.005 (6,407)$		

The number of breaths analyzed are given in parentheses

\*Two cigarettes were smoked during the first 15.5 minutes, on the average.

control period of the smoking day and that obtained after smoking started were not significantly different.

The mean incidences of fetal breathing during the control period of the smoking day and on the control day were  $64.8\% \pm 2.7$  and  $54.9\% \pm 8.0$ , respectively. Smoking had no significant effect on the incidence of breathing. There was also no change on the control day, and no significant difference between the two days (Fig. 5).

The number of fetal movements felt by the mother was significantly reduced during the first 30 minutes after smoking started (p < 0.01). The number was still reduced during the next 30 minutes, but returned to the control level between 60 and 90 minutes (Fig. 6). No significant change was observed on the control day.

Outcome of pregnancy. All 10 women were delivered of infants vaginally. Seven had spontaneous deliveries and three required forceps delivery, two because of signs of fetal distress and one because of thick meconium liquor (the fetal pH and heart rate pattern were normal). Seven deliveries were at term, and the average weight of the newborn neonates in this group was 3.21 kg (0.13 SD). One delivery was at 38 weeks' gestation (2.7 kg), one at 37 weeks (2.83 kg), and one at 36 weeks (1.93 kilograms). Apgar scores (1 and 5 minutes) were normal in nine babies. The premature baby born at 36 weeks required an immediate intubation because of apnea, but was extubated at 5 minutes with an Apgar score of 5.

#### Comment

It has been suggested that there is a long-term association between maternal cigarette smoking and fetal growth retardation, premature birth, and increased risk of stillbirth or neonatal death. <sup>10</sup> Both human studies <sup>11–13</sup> and animal experiments <sup>14–16</sup> have been interpreted as suggesting that fetal hypoxia, induced by nicotine or carbon monoxide in tobacco smoke, may be responsible. However, there is as yet no direct proof of these hypotheses.

Our latest findings serve to set straight the previous record and present a paradox. The A-scan ultrasound method is liable to misinterpretation on several counts, including bidirectional movement of the fetal chest with each breath. The Doppler method of identifying fetal breathing has been well validated in both sheep and man,<sup>8, 17, 18</sup> and has the advantage over real-time B-scans that breath intervals can be measured objectively to an acceptable degree of accuracy. The new findings show that the rate of fetal breathing is enhanced after cigarette smoking, with no change in incidence. The difference from the previous findings reported from this and other institutions is attributed to the difference in methods.

The paradox arises from the fact that maternal cigarette smoking is associated with a reduction in fetal

movements (as perceived by the mother) without a concomitant decrease in the incidence of breathing and with a decrease in mean breath interval. The former observation needs verification by an objective method. Let us for the sake of argument assume that it is true. At the present moment, the only mechanism by which fetal body or limb movements are reduced is believed to be hypoxia. However, hypoxia is known to be associated with prolonged apnea in fetal lambs or monkeys, and this was not observed in our study. It is possible, then, that additional factors other than hypoxia may influence fetal body movements. Indeed, no adequate studies have been executed to discriminate between hypoxemia, acidemia, and hypoglycemia as a cause of the disappearance of fetal movements prior to death in utero. Yet all three are known to be associated with prolonged apnea in fetal lambs.

The simplest explanation for the paradox is multifactorial, that the decrease in mean breath interval is attributed to, for instance, hypercapnia, whereas the decrease in perceived movements is due to some other cause, at present unknown. Two points may be made, first that it is unlikely on present evidence that the fetus is subject, as a result of maternal smoking, to hypoxemia sufficient to reduce body and limb movements, since breathing is maintained and the rate is increased. Second, it is unlikely that nicotine, which certainly crosses the placenta in man, <sup>19</sup> has a direct action on the carotid bodies. The latter are relatively insensitive to pharmacologic stimuli in fetal lambs near term, <sup>20. 21</sup> and maternal infusion of large doses does not appear to affect fetal breathing.

We are grateful for the help of Professor A. C. Turnbull and the consultants who made their patients available, and to the patients themselves who gave so much of their time and interest to the study.

#### REFERENCES

- 1. Boddy, K., and Robinson, J. S.: External method for detection of fetal breathing in utero, Lancet 2:1231, 1971.
- Wilds, P. L.: Observations of intrauterine fetal breathing movements, Am. J. Obstet. Gynecol. 131:315, 1978.
- Chapman, R. L. K., Dawes, G. S., Rurak, D. W., and Wilds, P. L.: Intermittent breathing before death in fetal lambs, Am. J. Obstet. Gynecol. 125:73, 1978.
- Gennser, G., Marsal, K., and Lindström, K.: Maternal smoking and fetal breathing movements, Am. J. Obstet. Gynecol. 123:861, 1975.
- Manning, F. A., and Feyerabend, C. I.: Cigarette smoking and fetal breathing movements, Br. J. Obstet. Gynaecol. 83:262, 1976.
- Manning, F., Walker, D., and Feyerabend, C.: The effect of nicotine on fetal breathing movements in conscious pregnant ewes, Obstet. Gynecol. 52:563, 1978.
- 7. Poore, E. R.: The relationship between fetal breathing movements as measured by thoracic pressure changes and the movement of the chest measured directly in vivo. Presented at the Fifth Conference on Fetal Breathing, Nijmegen, Holland, 1978.
- 8. Boyce, E. S., Dawes, G. S., Gough, J. D., and Poore, E. R.: Doppler ultrasound method for detecting human fetal breathing in utero, Br. Med. J. 2:17, 1976.
- Gough, J. D., and Poore, E. R.: A continuous Doppler ultrasound method for recording foetal breathing in utero, Ultrasound Med. Biol. In press.
- Pirani, B. B.: Smoking during pregnancy, Obstet. Gynecol. Surv. 33:1, 1978.
- Quigley, M. E., Sheehan, K. L., Wilkes, M. M., and Yen, S. S. C.: Elucidation of mechanisms for the deleterious effects of maternal smoking on fetal well-being. Pre-

- sented at the Twenty-fifth Annual Meeting of the Society for Gynecologic Investigation, Atlanta, Georgia, March 15-18, 1978.
- 12. Cole, P. V., Hawkins, L. V., and Roberts, D.: Smoking during pregnancy and its effect on the fetus, J. Obstet. Gynaecol. Br. Commonw. 79:782, 1972.
- 13. Longo, L. D.: The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant, AM. . Obstet. Gynecol. 129:69, 1977.
- 14. Suzuki, K., Horiguchi, T., Comas-Urrutia, A. C., Mueller-Heubach, E., Morishima, H. O., and Adamsons, K.: Pharmacologic effects of nicotine upon the fetus and mother in the rhesus monkey, Am. J. OBSTET. GYNECOL. 111:1092, 1971.
- 15. Resnik, R., Brink, G. W., and Wilkes, M. M.: Catecholamine-mediated reduction in uterine blood flow following nicotine infusion in the pregnant ewe. Presented at the Twenty-fifth Annual Meeting of the Society for Gynecologic Investigation, Atlanta, Georgia, March 15-18, 1978.
- 16. Kirschbaum, J. H., Dilts, P. V., Jr., and Brinkman, C. R.:

- Some acute effects of smoking in sheep and their fetuses, Obstet. Gynecol. 35:527, 1970.
- 17. Gough, J. D., and Poore, E. R.: Directional Doppler measurements of fetal breathing, J. Physiol. (Lond.) 272:12P, 1977.
- 18. Goodman, J. D. S., and Mantell, C.: Two means of measuring fetal breathing movements by the Doppler method. Presented at the Fifth Conference on Fetal Breathing, Nijmegen, Holland, 1978.
- 19. Van Vanakis, H., Langore, J. J., and Milunski, A.: Nicotine and cotinine in the amniotic fluid of smokers in the second trimester of pregnancy, Am. J. OBSTET. Gynecol. 120:64, 1974.
- 20. Dawes, G. S., Lewis, B. V., Milligan, J. E., Roach, M. R., and Talner, N. S.: Vasomotor responses in the hind limbs of fetal and newborn lambs to asphyxia and aortic chemoreceptor stimulation, J. Physiol. 195:55, 1968.
- 21. Dawes, G. S., Duncan, S. L. B., Lewis, B. V., Merlet, C. L., Owen-Thomas, J. B., and Reeves, J. T.: Cyanide stimulation of the systemic arterial chemoreceptors in fetal lambs, J. Physiol. 201:117, 1969.

### Time-lapse study of normal human trophoblast in vitro

JUDITH LUECK, B.S. SILVIO ALADJEM, M.D.

Chicago and Maywood, Illinois

Time-lapse photographic observations of normal human trophoblast in vitro were made possible through the development of a new technique that allows for prolonged trophoblast culturing without stromal growth. Y body fluorescence and determinations of human placental lactogen (hPL) were used to confirm the specificity and viability of the cells in culture. Epithelioid cells (cytotrophoblast) with agranular cytoplasm, binucleated moderately granulated cells, and multinucleated heavily granulated syncytial masses were observed. The cytotrophoblast was observed in mitosis, whereas the syncytium showed strand formation and reabsorption, along with mass movement of cells at time of confluency. This technique should stimulate a renewed interest in the in vitro studies of normal human trophoblast. (AM. J. OBSTET. GYNECOL. 138:288, 1980.)

STUDIES OF normal human trophoblast in tissue culture<sup>1</sup> have had limited application as a result of the short survival of trophoblastic cells and stromal overgrowth. Consequently, it has been suggested that in vitro experimentation with human trophoblast should be carried out on short-term (7 to 10 days) cultures only.<sup>2</sup> In 1975, Aladjem and Lueck<sup>3</sup> first reported successful inhibition of stromal growth in cultures of normal trophoblast. Further refinement of this technique<sup>4</sup> now permits long-term (8 months) cultures without stromal growth. This report describes observations made by time-lapse photography of normal human trophoblast in vitro.

#### Method and material

Sixteen placentas were obtained from normal pregnancies at term (38 to 42 weeks) under aseptic conditions from scheduled repeat cesarean sections. Immediately after delivery, the maternal aspect of the placenta was inspected for areas of gross pathologic conditions (infarction, calcification, ect.). From

From the Department of Physiology and Biophysics, University of Illinois Medical Center, Abraham Lincoln School of Medicine, Chicago, and the Department of Obstetrics and Gynecology, Loyola Stritch School of Medicine, Maywood.

This work was supported in part by BRSG Grant No. 447-10, Loyola Stritch School of Medicine.

Received for publication March 18, 1980.

Accepted June 11, 1980.

Reprint requests: Silvio Aladjem, M.D., 2160 South First Ave., Maywood, Illinois 60153.

normal-appearing areas, and after confirmation by phase-contrast microscopic study of fresh tissue specimens, approximately 20 grams of tissue (1 gram pieces) were sampled from the chorionic to the decidual plate and placed in sterile 0.1% trypsin in versene. The tissue was then minced with iridectomy scissors into pieces 1 cubic millimeter in size. Suspensions of cells were prepared by placing the pieces into 250 ml trypsinization flasks with 150 ml of 0.1% trypsin in versene and agitating with a magnetic stirrer at slow speed for 1 hour. The cell suspension was then decanted into 50 ml centrifuge tubes and spun at 1,200 rpm for 15 minutes. The supernatant was removed and the cells were resuspended in 10 ml of Ham's F-12 media, 30% fetal calf serum with 100 units of penicillin and 100  $\mu$ g of streptomycin per milliliter.\* Trypan blue dye exclusion was used for viability testing.

Approximately 10 ml of the resultant suspension was placed in a 250 ml Falcon flask (high-density plating). The flasks were tightly sealed and placed in an incubator at 37° C and left undisturbed for 14 days, at the end of which time half the media was exchanged and the flasks were again tightly sealed and incubated at 37° C. After 21 days in vitro the flasks were examined for growth. If trophoblastic proliferation had begun (20 to 28 days in vitro), the cultures were refed, capped loosely, and placed in a conventional way in an incubator at a 37° C with 95% air and 5% CO<sub>2</sub>. Cultures were subsequently fed once a week. Subcultures of confluent monolayers were obtained with 0.1% trypsin

\*GIBCO, Grand Island, New York.

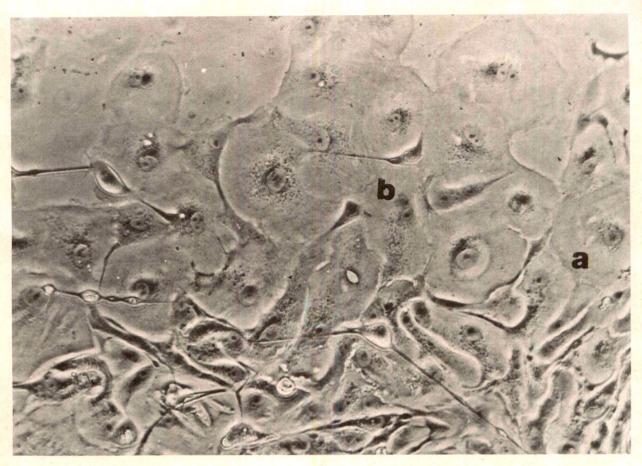


Fig. 1. Normal human trophoblast 42 days in vitro (×236). a, Epithelioid cell (cytotrophoblast) with agranular cytoplasm and single nucleus. b, Binucleated cell with moderate granulation of the cytoplasm.

in versene. Y body fluorescence was performed in placentas from male infants after the method of Lueck and Zaneveld.<sup>5</sup> Radioimmunoassay of levels of human placental lactogen\* (hPL) were performed on the culture media obtained at the time of feeding. A Nikon phase-contrast inverted MS microscope and CFMA cinematography equipment, at a speed of four frames per minute with Kodak Plus-X 16 mm reversal films at 100×, were used for time-lapse photography.

#### Results

Trypan blue dye exclusion testing performed after trypinization showed an 87% viability. After 20 to 28 days, 16% of established cultures showed no signs of growth. In the other 84% epithelioid cells that had a "fried egg" appearance were observed, firmly adherent to the bottom of the flasks. The cytoplasm of the cells was agranular, and the nucleus contained one or two prominent nucleoli (Fig. 1). Seven to 10 days later, syn-

\*Pharmacia Diagnostics, Piscataway, New Jersey.

cytial masses with multiple nuclei were present, and in contrast to the epithelioid cells their cytoplasm was heavily granulated (Fig. 2). Transitional zones between the agranulated epithelioid cells and granulated syncytial masses could be identified (Fig. 1). Characteristic of this area was an increase in granulation of the cytoplasm, with a concomitant increase in the number of nuclei. There were no fibroblastic stromal cells.

At the time of confluency, cells in cultures from placentas of male infants showed an 85% Y body fluorescence. Levels of hPL in the culture media increased from an initial value of 1.7 ( $\pm 0.3$ )  $\mu$ g/ml at 14 days of culture to 2.7 ( $\pm 0.5$ )  $\mu$ g/ml at confluency.

During the 8 months in culture, the flasks were subcultured three times. Cultures could not be maintained after the fourth attempted passage.

Time-lapse photography showed the epithelioid cells (cytotrophoblast) in active mitosis, occurring within approximately 2 hours (Fig. 3). During this process the cells detached from the plastic surface and became rounded (Fig. 3, b). In metaphase, chromosomal

290 Lueck and Aladjem October 1, 1980
Am. J. Obstet. Gynecol.

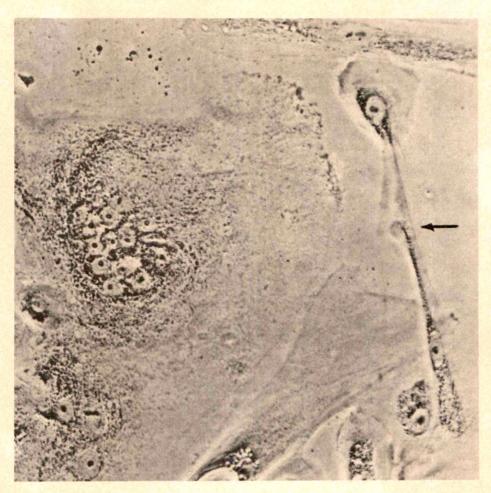


Fig. 2. Normal human trophoblast 65 days in vitro ( $\times$ 354). Note multinucleated syncytial mass with 11 nuclei, and heavy granulation of the cytoplasm. Compare with cells a and b in Fig. 1. Arrow points toward early stage of syncytial strand formations (see text).

alignment could be observed. After telophasic separation (Fig. 3, d), the two daughter cells were seen to flatten out on the plastic surface and assume epithelioid morphologic features. Syncytial strand formation occurred when syncytial masses migrated in two different directions (Fig. 2). The strands were eventually reabsorbed back into one of the syncytial masses. As confluency was reached, mass movements of cell monolayers could be observed. Trophoblastic nuclei showed rotational and translational movement within the cytoplasm.

#### Comment

This new method promotes the growth of trophoblastic cells while inhibiting stromal growth by a simple and rather unorthodox variation in tissue culture technique, i.e., high-density plating and hypoxia during the first 3 weeks in culture. For the seasoned tissue culturist, the mere "appearance" of the flasks by day

14, with dark brown culture media and tissue floating as a result of high-density plating, would be unacceptable according to traditional techniques of culturing. This new method will test the culturist's patience and stamina, but restraint will be rewarded, since between day 21 and day 28, 84% of the flasks will begin to show the classic "fried egg" appearance of healthy adherent epithelioid cells. At that time, traditional tissue culture techniques are followed and result in confluent cultures of trophoblastic cells, without stromal growth or overgrowth. Teleologically, it is not surprising that the trophoblast survives the initial 14 to 21 days of hypoxia but the stromal elements do not. Y body fluorescence studies of trophoblast from male infants and hPL values of the media confirm that the cells observed are trophoblast.

Thiede<sup>1</sup> described three types of cells in culture: the epithelioid, probably cytotrophoblast; the multinucleated, probably syncytium; and the fibroblasts. In our

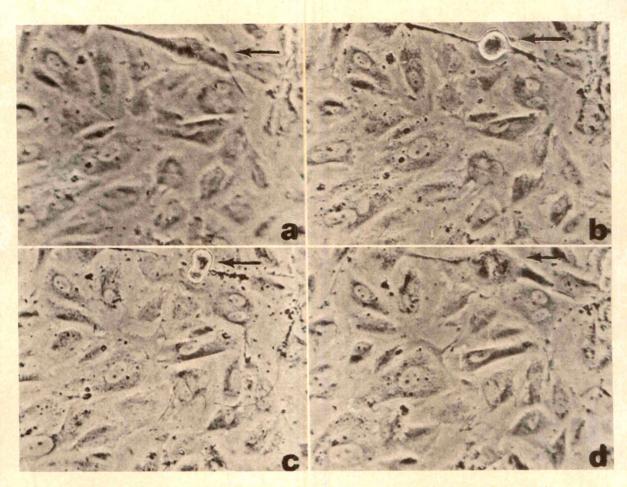


Fig. 3. Composite of time-lapse photography of normal human trophoblast 57 days in vitro (×127). a, Frame No. 1404. Arrow points to cell in the initial stage of mitosis. b, Frame No. 1494, 22.5 minutes later. Arrow points to characteristic metaphase stage of cell in Frame a. c, Frame No. 1728, 58.5 minutes after b. Arrow points to cell in telephase. d, Frame No. 1908, 45 minutes after c. Arrow points to two resulting daughter cells.

studies, the "fried egg" cell, a large epithelioid cell with single nucleus, had the morphologic characteristics of cytotrophoblast, whereas the multinucleated cells were characteristic of syncytium. There were no fibroblasts or other stromal cells in our cultures. The similarity between Thiede's study and ours, however, is only apparent. Most likely, the cells observed in Thiede's study were not the result of active in vitro proliferation, but rather the result of dissociation of cells with a limited viability in culture until completely overtaken by actively growing stromal cells. This contention is supported by Valenti's6 time-lapse studies of normal trophoblast in vitro. He did not observe mitosis in cultures and noted the disappearance of both epithelioid and syncytial cells by day 10, with the stromal cells overgrowing the cultures. Our time-lapse studies revealed active mitosis in the epithelioid cells (cytotrophoblast). Syncytial masses could be observed forming strands. Nuclear spinning and translational movement of nuclei within the cytoplasm, as well as mass movements of the cell monolayers, were seen. Such activity became increasingly apparent as confluency was reached, and determinations of hPL confirmed the metabolic viability of the cells in culture, as well as biologic specificity. The morphologic variation observed between the agranular cytoplasm of the epithelioid cells, the binucleated moderately granulated cells, and the multinucleated heavy granulated syncytial masses may have represented the in vitro differentiation of cytotrophoblast into syncytiotrophoblast with an intermediate cell. The granulations may have represented secretory activity.

It should be noticed that this technique has not yet been successfully applied to the culturing of early trophoblast, although it has been successful with trophoblast obtained after the thirtieth week of gestation. Why trophoblast from different gestational ages be292 Lueck and Aladjem October 1, 1980
Am. J. Obstet. Gynecol.

haves differently in culture is not known. Also, the duration of cultures could not be maintained beyond four passages over an 8 month period.

Studies to characterize in vitro metabolic activity of the trophoblast from both normal and abnormal pregnancies are currently in progress in our laboratory. It is hoped that this new methodology will stimulate a renewed interest in the in vitro studies of normal human trophoblast.

#### REFERENCES

- Thiede, H.: Studies of the human trophoblast in tissue culture. I. Culture method and histochemical studies, Am. J. Obstet. Gynecol. 79:636, 1960.
- Taylor, P. V., and Hancock, K. W.: Viability of human trophoblast in vitro, J. Obstet. Gynaecol. Br. Commonw. 80:834, 1973.
- 3. Aladjem, S., Lueck, J., Harris, J., and Wynn, R.: Culture of human placenta, *in* Campodonico, I., editor: Proceedings of the Sixteenth Chilean Congress of Obstetrics and Gynecology, Santiago, Chile, 1975, p. 25.
- Aladjem, S., Lueck, J., and Tsai, A.: A method for prolonged in vitro culture of normal human trophoblast, Fed. Am. Soc. Exp. Biol. 39:506, 1980.
- Lueck, J., and Zaneveld, L.: Cytogenetics of human sperm, in Hafez, F., editor: Techniques of Human Andrology, Amsterdam, 1977, North Holland Publisher, p. 203.
- 6. Valenti, C.: Time lapse photography of placental cells in tissue culture, *in* Thiede, H., editor: Transcripts of the Second Rochester Trophoblast Conference, 1963, p. 250.

### Maternal and fetal immune responses to human trophoblast antigens

PAMELA V. TAYLOR\*

Leeds, England

Maternal and fetal cord leukocytes were tested in cytotoxicity assays against cultured autochthonous trophoblast cells. Significant lysis occurred with both categories of leukocyte, but the degree of cytotoxicity was less with fetal cells. These results suggest reduced fetal immunocompetence, the presence of fetal suppressor cells, or the presence of histocompatibility factors in trophoblast. Both fetal and maternal sera exhibited blocking activity in these tests and the source of this activity is discussed. The presence of particulate placental antigen inhibited trophoblast lysis by maternal leukocytes and no difference was observed between the effects of autochthonous and heterologous antigens. (Am. J. Obstet. Gynecol. 138:293, 1980.)

MATERNAL CELL-MEDIATED immunity to human fetal antigens has been demonstrated by an assay of the macrophage-migration inhibition factor with both neonatal lymphocytes1 and placental extract2 used as antigens and by lymphocytotoxicity tests with cultured trophoblast cells used as targets.3 Serum factors modifying such immune reactions have been shown to be present in both maternal4. 5 and neonatal6 sera. Uncertainty remains as to the specificity of the response and the nature of the trophoblast antigens to which it is directed; whether these are tissue-specific, associated with some stage of ontogeny, or consist of histocompatibility factors is unknown. In this study lymphocytotoxicity assays were performed in an attempt to establish the specificity of the response by testing the effects of fetal leukocytes on autochthonous trophoblast cells and comparing blocking by maternal and fetal sera.

The response of maternal lymphocytes to cultured trophoblast apparently involves cellular contact,<sup>3</sup> the recognition phase or the immune lysis possibly depending on binding of lymphocyte receptors to trophoblast surface antigens so that the response should be inhib-

From the Department of Obstetrics and Gynaecology, University of Leeds.

Supported by the Edgar Research Fellowship, awarded to Professor D. M. Jenkins.

Received for publication February 1, 1980.

Revised April 9, 1980.

Accepted May 29, 1980.

Reprint requests: Pamela V. Taylor, Department of Obstetrics and Gynecology, University of Leeds, Leeds, England LS2 9NG.

\*Research Fellow.

ited in the presence of particulate membrane antigen prepared from placental chorionic villous tissue. This inhibition test was used to investigate the nature of trophoblast antigenicity by comparing the effects of autochthonous and heterologous placental antigens. If these consist of histocompatibility factors no inhibition would be expected with heterologous placentas, except in individuals possessing cross-reacting antigens, which could be checked by tissue typing.

#### Material and methods

Trophoblast cultures were prepared from normal term placentas by trypsinization of chorionic villous tissue by the method of Thiede and Rudolph.<sup>7</sup> The culture medium consisted of 10% fetal calf serum (Wellcome) or maternal or fetal cord serum, where appropriate, in medium 199 (Wellcome), and the cells were grown on glass coverslips in Leighton tubes at an initial concentration of  $1 \times 10^6$  cells per culture.

At the time of culturing one entire cotyledon was removed from the placenta; the fetal membrane was removed, and a microsomal fraction was prepared by homogenization and differential centrifugation according to the method of Nairn and associates. The fraction was resuspended in phosphate-buffered saline (pH 7.1) at a concentration of approximately 10,000  $\mu$ g/ml and stored at  $-20^{\circ}$  C. This antigen was nonimmunogenic in lymphocyte transformation tests toward either the mother's or unrelated maternal lymphocytes at a concentration of  $100 \ \mu$ g/ml, the concentration used in the experiments.

Heparinized (200 U/ml) and unheparinized maternal venous and fetal cord blood specimens were obtained at the time of delivery. Fetal and maternal sera

**Table I.** Numbers of surviving trophoblast cells in cultures incubated with maternal and fetal leukocytes

Patient No.	1. Medium control cultures*	2. Maternal leukocytes added	3. Fetal leukocytes added
1	330	67	184
2	17	4	18
3	221	62	154
4	363	36	180
5	201	97	121
6	366	22	91
7	59	17	20
8	463	203	225
9	116	119	171
10	338	249	270
11	429	184	211
12	576	0	180
13	511	115	163

<sup>\*</sup>Fetal calf serum medium.

Significances of difference between: I and 2 = p < 0.01, between I and 3 = p < 0.01, and between 2 and 3 = p < 0.05.

**Table II.** Numbers of surviving trophoblast cells in cultures incubated with maternal and fetal leukocytes in the presence of maternal serum

Patient No.	1. Medium control cultures*	2. Maternal leukocytes added	3. Fetal leukocytes added
1	376	432	213
2	47	101	131
3	343	351	256
4	359	172	402
5	340	368	287
6	357	277	326
7	246	189	290
8	203	141	330
9	401	497	430
10	448	627	702
11	751	672	711
12	1,079	1,126	1,142
13	535	468	277

<sup>\*</sup>Maternal serum medium.

**Table III.** Numbers of surviving trophoblast cells in cultures incubated with maternal and fetal leukocytes in the presence of fetal cord serum

Patient No.	1. Medium control cultures*	2. Maternal leukocytes added	3. Fetal leukocytes added
1	306	454	208
2	32	24	42
3	309	321	112
4	365	131	429
5	451	273	177
6	373	347	310
7	229	82	108
12	1,182	890	1,011
13	511	366	322

<sup>\*</sup>Fetal cord serum medium.

were separated and stored overnight at 4° to 8° C. An aliquot of the heparinized specimens was used to type both maternal and fetal lymphocytes for 25 human lymphocyte A antigens with at least two antisera used for each. A leukocyte-rich fraction was obtained from the remaining aliquots by sedimentation with one third the volume of plasmagel for approximately 30 minutes at 37° C and stored overnight at 4° to 8° C.

Twenty-four hours after the trophoblast cultures were started, the fetal and maternal leukocytes were washed six times in medium 199 and 4 × 106 viable cells (tested by exclusion of trypan blue) added per culture to separate groups of cultures in either a fetal calf serum or a maternal or fetal cord serum medium. Control cultures received fresh medium containing the appropriate serum with no leukocytes added. Additional groups of cultures having maternal leukocytes added in fetal calf serum medium also received 100 µg of either autologous or heterologous microsomal fraction per culture. A minimum of three cultures were included in each group. After 5 days' incubation the cultures were terminated and numbers of surviving trophoblast cells were assessed as previously described.3 Statistical analysis of the data was performed by applying Student's t test.

#### Results

A total of 20 normal term placentas from women of varying parity were examined. A comparison of the cytotoxic effects of maternal and fetal leukocytes on autochthonous trophoblast cells is shown in Table I. Significant reduction in trophoblast cell numbers occurred in both groups. However, the cytotoxic effect of fetal cells was less than that of maternal cells and this difference was statistically significant (see Table I). The presence of maternal serum reduced trophoblast lysis by both maternal and fetal leukocytes (Table II) and a similar effect was observed in the presence of fetal cord serum (Table III). The presence of placental antigen in the cultures significantly reduced trophoblast cell lysis and there was apparently no difference in the degree of inhibition achieved with autochthonous and heterologous preparations (see Table IV).

#### Comment

Maternal lymphocytotoxicity toward fetal trophoblast cells has been demonstrated in vitro<sup>3, 9, 10</sup> and the specificity of the cytotoxic effect was investigated with lymphocytes from male and female donors, the latter both nulliparous and undergoing normal term delivery.<sup>3</sup> The period of incubation in the present study, chosen to facilitate cell counting, may not have pre-

There were no significant differences.

There were no significant differences.

Table IV. Effect of autochthonous and heterologous placental antigen on maternal cell-mediated cytotoxicity toward trophoblast cells and relationship with histocompatibility typing

Patient No.	1. Medium control cultures*	2. Maternal lymphocytes added	3. Maternal lymphocytes plus autologous antige <mark>a</mark>	4. Maternal lymphocytes plus heterologous antigen	Human lymphocyte antigen typing (A, mother; B, baby)	No. of matched antigens
2	N.T.	N.T.	N.T.	N.T.	A. 2,W27	_
5	201	97	185	134 (2‡)	B. N.T.† A. 2,12,W10 B. 2,W10	. 1
13	511	115	464	523 (2)	A. 2,W14 B. 2,3,W14	1
14	683	467	661	490 (13)	A. 1,2,8,12	1
15	86	48	79	73 (14)	B. 2,11,12 A. 11,5	1
16	324	231	267	200 (15)	B. 1,11,5,8 A. 2,12,W14	0
17	417	222	226	207 (16)	B. 3,W14,W18 A. W28,12,W5	0
18	485	257	423	439 (17)	B. W28,W5 A. 1,2,7	0
19	113	80	123	126 (18)	B. 1,2,W15 A. 2,7,W15	2
20	170	136	125	110 (19)	B. 2,W15,W17 A. 2,3,W10,W17 B. N.T.†	2

Significance of difference between 1 and 2 = p < 0.05. There were no other significant differences. N.T.: Not typed.

cluded sensitization in vitro. Treatment with trypsin reduces the amount of mucoprotein present on the trophoblast cell surface but this is resynthesized rapidly in vitro<sup>3</sup> so that any sensitization occurring is probably not to altered trophoblast. However, correlation with maternal immune responses occurring in normal pregnancy remains unclear but the test does suggest the presence of antigens on the trophoblast surface and, moreover, that fetal leukocytes recognize some trophoblast antigens as foreign and are capable of immune reactivity toward them. Reduction of trophoblast cell numbers in the test cultures was not due to depletion of nutrients in the medium; cell-free supernatants from mixed cultures of trophoblast cells and either maternal or fetal leukocytes removed on days 3, 4, and 5 supported trophoblast cell growth to an extent indistinguishable from control cultures in fresh medium. The quantitative difference between maternal and fetal cell-mediated immunity may be associated with a reduced fetal immunocompetence. The evidence for this is conflicting as far as response to phytohemagglutinin is concerned, with reports of greater<sup>11</sup> and reduced<sup>12</sup> responsiveness. Neither of these studies allowed for serum effects. Ayoub and Kasakura<sup>6</sup> observed the suppressed response of fetal lymphocytes in both adult and fetal plasma but it was suggested that traces of plasma factors may have remained on the lymphocyte surface. The leukocytes in the present study were washed extensively before testing so that the reduced reactivity of fetal cells may have been a consequence of the heterogeneity of trophoblast antigens, possibly including histocompatibility factors to which the fetal cells would not respond. Another possibility concerns the presence of a population of suppressor T cells in fetal blood which may modulate the response to trophoblast antigens. It has been shown that adult lymphocytes require activation by immune complexes before significant suppressor activity can be detected.13 The fetal cells may have been activated by maternally derived immune complexes so that their immunosuppressive effect was apparent in cultures containing only fetal calf serum. Of course the maternal lymphocytes would be primed in the same way and the quantitative difference in cell-mediated immunity between maternal and fetal lymphocytes may reflect the finding that there are many more suppressor T cells in cord blood than in adult blood.14

The immunosuppressive effect of maternal serum may be due to both specific factors such as antibody or immune complexes and the nonspecific suppressive effects of, for example, pregnancy hormones.3, 4 These results demonstrate that such factors block fetal lym-

<sup>\*</sup>Fetal calf serum medium.

<sup>†</sup>Human lymphocyte antigen typing of mother used.

<sup>‡</sup>Numbers in parentheses indicate patients donating heterologous antigen.

phocyte-mediated cytotoxicity as well as maternal lymphocytes, suggesting that they have their effect both on the lymphocyte and at the trophoblast surface. Maternal immunoglobulin G-crossing the placenta may contribute to the observed blocking effect of fetal serum. Immunosuppressive maternal  $\alpha$ - and  $\beta$ -proteins probably do not cross the placenta<sup>15</sup> but  $\alpha_1$ -fetoglycoprotein has been shown to be immunosuppressive<sup>16</sup> and is still detectable in newborn infants. Therefore, there may be both maternal and fetal contributions to the blocking effect of fetal serum.

It has been shown<sup>17</sup> that binding of mouse lymphocytes to target cell surface antigens was inhibited in the presence of nonimmunogenic particulate and soluble membrane antigens, the inhibiting effect being in this case strain-specific. If the trophoblast cultures are taken as a whole, inhibition was achieved equally with autochthonous and heterologous antigen. The mean number of matched antigens for the pairs tested was

0.88 and there did not appear to be any correlation between degree of inhibition and number of matched antigens in any individual case (Table IV). This might suggest that histocompatibility factors are not the recognized elements in the reaction of maternal lymphocytes to trophoblast cells but that tissue-specific antigens are involved. However, this would not be consistent with the data from the lymphocytotoxicity tests, and this finding may be associated with the method of preparation of the placental antigen, involving mechanical disruption of the chorionic villous tissue and probably giving rise to a very heterogenous mixture of antigens. A method of preparing relatively pure trophoblast surface membrane has been developed 18 and studies with this more specific preparation in an inhibition assay of trophoblast antigens are under way.

I thank Mr. J. E. Wood for technical help, and the Regional Blood Transfusion Service, Bridle Path, Leeds, for the tissue typing.

#### REFERENCES

- Rocklin, R. E., Zuckerman, J. E., Alport, E., and David, J. R.: Effect of multiparity on human maternal hypersensitivity to fetal antigens, Nature 241:130, 1973.
- 2. Youtananukorn, V., and Matangkasombut, P.: Human maternal cell-mediated immune reaction to placental antigens, Clin. Exp. Immunol. 11:549, 1972.
- Taylor, P. V., and Hancock, K. W.: Antigenicity of trophoblast and some possible antigen-masking effects during pregnancy, Immunology 28:973, 1975.
- 4. Youtananukorn, V., and Matangkasombut, P.: Specific plasma factors blocking human maternal cell-mediated immune reaction to placental antigens, Nature New Biol. 242:110, 1973.
- Taylor, P. V., Hancock, K. W., and Scott, J. S.: The possible role of serum factors in masking the antigenicity of human trophoblast in vitro, in Proceedings of First International Congress on Immunology in Obstetrics and Gynaecology, Amsterdam, 1973, Excerpta Medica, International Congress Series No. 281, p. 18.
- Ayoub, J., and Kasakura, S.: In vitro response of fetal lymphocytes to PHA and a plasma factor which suppresses the PHA response of adult lymphocytes, Clin. Exp. Immunol. 8:427, 1971.
- Thiede, H. A., and Rudolph, J. H.: A method for obtaining monolayer cultures of human fetal cells from term placentas, Proc. Soc. Exp. Biol. Med. 107:565, 1961.
- 8. Nairn, R. C., Richmond, H. G., McEntegart, M. G., and Fothergill, S. E.: Immunological differences between normal and malignant cells, Br. Med. J. 2:1335, 1960.
- Currie, G. A.: Immunological studies of trophoblast in vitro, Br. J. Obstet. Gynaecol. 74:841, 1967.

- Douthwaite, R. M., and Urbach, G. I.: In vitro antigenicity of trophoblast, Am. J. Obstet. Gynecol. 109:1023, 1971.
- 11. Lindahl-Kiessling, K., and Book, J. A.: Effects of PHA on leucocytes, Lancet 2:591, 1964.
- Jones, W. R.: In vitro transformation of fetal lymphocytes, Am. J. Obstet. Gynecol. 104:586, 1969.
- Moretta, L., Webb, S. R., Grossi, C. E., Lydyard, P. M., and Cooper, M.D.: Functional analysis of two human T-cell subpopulations: help and suppression of B-cell responses by T cells bearing receptors for IgM or IgG, J. Exp. Med. 146:184, 1977.
- Hayward, A. R., and Lawton, A. R.: Induction of plasma cell differentiation of human fetal lymphocytes: evidence for functional immaturity of T and B cells, J. Immunol. 119:1213, 1977.
- 15. Brambell, F. W. R.: The Transmission of Passive Immunity from Mother to Young, Amsterdam, 1970, North Holland Publishing Company, p. 254.
- Holland Publishing Company, p. 254.
  16. Cooperband, S. R., Bonderik, H., Schmidt, K., and Marnick, J. A.: Transformation of human lymphocytes: inhibition by homologous α-globulin, Science 159:1243, 1968.
- Feldman, M., Cohen, I. R., and Ulekerke, H.: T-cell mediated immunity in vitro: an analysis of antigen recognition and target cell lysis, Transplant. Rev. 12:57, 1972.
- Smith, N. C., Brush, M. G., and Luckett, S.: Preparation of human placental villous surface membrane, Nature 252:302, 1974.

### Ultrasound measurement of fetal limb bones

JOHN T. QUEENAN GREGORY D. O'BRIEN STUART CAMPBELL

London, England

A study was made of 41 patients with known menstrual dates in whom the duration of gestation, as determined by physical examination and ultrasound scan, corresponded with those dates. Examination of the fetal limb lengths was done every 1 to 3 weeks, starting at 8 weeks' gestation. A Kretz Combison 100 ultrasound sector scanner with a 2.5 MHz transducer (velocity = 1,540 meters per second) was used. A freeze frame was used when the full bone length was visualized, and then electronic calipers were employed to measure its full length. Serial measurements of the humerus and femur and the radius-ulna and tibia-fibula complexes were made. The values were expressed as means ± 2 standard deviations for each week of gestation. The growth of the fetal limb bones was linear from 12 through 22 weeks' gestation, but the various bones appeared to grow at different rates. The femur was the first to be well defined and the easiest to measure with reproducibility. All of the limb bone lengths correlate with gestational age and may serve as indicators of skeletal dysplasia. A patient who was delivered of an infant affected with diastrophic dwarfism syndrome was diagnosed at 16 weeks' gestation to have a fetus affected with this problem. Two other patients whose pregnancies were at risk for skeletal dysplasias were correctly diagnosed to be normal. (Am. J. Obstet. Gynecol. 138:297, 1980.)

WITH THE NEWER focused real-time ultrasound scanners it is possible to visualize and measure fetal bones accurately in early pregnancy. During this period, the fetus is extremely active, 1 but despite this mobility, the limb bones can be defined in full outline by the use of real-time scanning and freeze-frame. A standard curve for limb bone measurements in early pregnancy is described, thus providing a new parameter for studying fetal development.

#### Material and methods

Forty-one pregnant patients were studied. The menstrual dates were known, and the duration of gestation, determined by physical examination and ultrasound scan, corresponded with those dates. Examination of the fetal limb bones was done every 1 to 3 weeks, starting at 8 weeks' gestation. When possible, bilateral measurements were obtained.

From the Department of Obstetrics and Gynecology, King's College Hospital.

Received for publication April 11, 1980.

Accepted May 1, 1980.

Reprint requests: John T. Queenan, M.D., Department of Obstetrics and Gynecology, Georgetown University School of Medicine, 3800 Reservoir Road, N. W., Washington, D. C. 20007.

The ultrasound examinations were done with a Kretz Combison 100 sector scanner with the use of a 2.5 MHz transducer (velocity = 1,540 meters per second). A freeze-frame was used when the full fetal limb bone length was visualized, and then electronic calipers were employed to measure its length.

Serial measurements of the humerus and femur, and of the radius-ulna and tibia-fibula complexes were made. Each bone had to be examined in several planes and from different angles in order to ensure that the ultrasound image of the entire bone had been visualized, and that only that bone had been included in the measurements. Errors in both directions, shortening or lengthening, were possible if angulation of the transducer took a tangential section of the bone or superimposed adjacent bones.

The femur was the earliest to be well defined and was the easiest to measure with excellent reproducibility<sup>2</sup> (Fig. 1). Often, the iliac bone would be superimposed, and it was necessary to distinguish this bone so that it would not be included in measurement of the femur. The femur was identified from 8 weeks' gestation and could be measured accurately from 10 weeks' gestation. Mild physiologic "bowing" of the femur was also observed quite often after 18 weeks' gestation. The tibia-fibula and the radius-ulna were measured as "com-

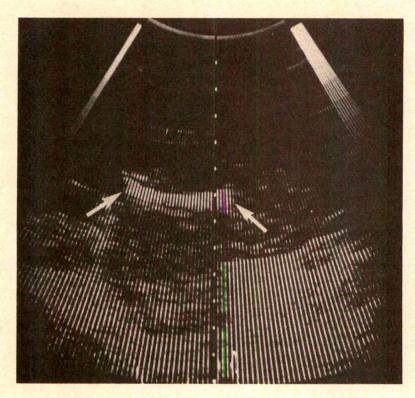
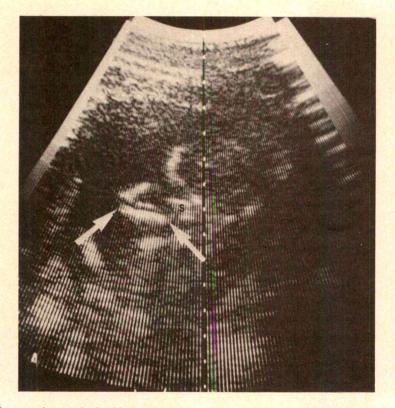


Fig. 1. Ultrasound scan of a fetal femur at 22 weeks' gestation (arrows).



**Fig. 2.** Ultrasound scan of a fetal humerus at 15 weeks' gestation (*arrows*). Note the proximity of the scapula (*S*).

Table I. Comparison of ultrasound measurements with x-ray measurements, taken to the nearest millimeter, of the limb lengths of aborted fetuses

	Femur (mm)				Radius-ulna (mm)		Tibia-fibula (mm)	
Gestational age of fetus	X-ray	Ultrasound	X-ray	Ultrasound	X-ray	Ultrasound	X-ray	Ultrasound
15 1	19	20	19	19	17	19	15	15
15 wk	32	33	30	32	29	31	28	29
19 wk and 3 days	34	34	32	33	31.5	32	30	29
20 wk and 1 day 23 wk and 3 days	47	46	42	43	42	40	39	41

Table II Femur

Weeks' gestation	Arithmetic mean (mm)	±2 SD (mm)	No. of determinations
11	10.2	1.8	9
12	12.5	2.4	15
13	14.8	4.5	17
14	17.9	3.7	15
15	20.8	3.1	20
16	24.1	3.6	16
17	26.4	2.9	18
18	29.4	2.3	15
19	32.3	3.0	21
20	36.1	3.8	17
21	39.7	3.5	14
22	42.8	3.4	12

Weeks' gestation	Arithmetic mean (mm)	±2 SD (mm)	No. of determinations
11	9.2	1.5	9
12	11.1	3.2	15
13	12.9	3.8	16
14	16.4	4.5	13
15	19.8	4.3	18
16	22.8	2.9	15
17	24.9	3.4	12
18	27.1	3.0	14
19	29.5	3.8	19
20	33.8	4.6	13
21	35.0	3.4	10
22	38.7	3.8	10

Table III Humerus

Weeks' gestation	Arithmetic mean (mm)	±2 SD (mm)	No. of determinations
11	9.7	1.5	10
12	12.0	3.1	14
13	15.1	5.9	17
14	18.0	3.4	13
15	20.6	4.2	17
16	24.0	3.2	12
17	26.0	3.5	11
18	28.7	2.0	13
19	31.0	3.9	17
20	34.9	3.9	14
21	36.4	4.3	12
22	40.4	3.6	9

Table V Tibia-fibula

Table IV. Radius-ulna

Weeks' gestation	Arithmetic mean (mm)	±2 SD (mm)	No. of determinations
11	9.0	2.9	6
12	11.1	2.9	10
13	12.1	4.8	12
14	14.1	2.8	10
15	17.8	4.1	15
16	20.2	4.8	11
17	23.4	3.9	13
18	25.2	3.7	9
19	28.3	4.2	13
20	30.7	2.5	11
21	33.9	4.9	14
22	37.3	4.2	12

plexes" because it was difficult to measure a single bone. The ulna appeared to be slightly longer than the radius, and, thus, difficult to measure independent of it. The radius-ulna and tibia-fibula complexes were easier to measure in the early stages of pregnancy, but as the gestational age increased, the extreme mobility of these distal bones made difficult the measurement of the full length of the complex. The humerus was the bone most difficult to define accurately, because of its proximity to the chest wall and its apparent continuity with the scapula and clavicle (Fig. 2).

On each occasion, several measurements were made

on each limb until three closely corresponding results were obtained within a 2-mm range. An average of the three was then used. Each examination took approximately 15 minutes, although with a very active fetus it could take longer.

To substantiate the validity of our technique, we scanned four patients who were undergoing induced abortion with normal pregnancies at known gestations from 15 to 23 weeks. The period of gestation was confirmed by ultrasound biparietal diameter, and then measurements of the limbs were made. Roentgenograms of the aborted fetuses were performed, and

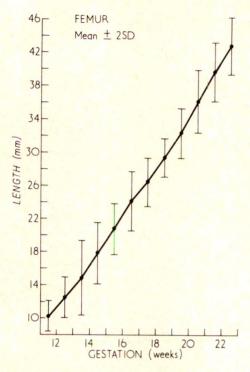


Fig. 3. Length of femur plotted against weeks of gestation.

measurements of bone lengths were made. The ultrasound measurements of the limb bones compared favorably with the limb bone lengths visualized on x-ray films. The comparison of these measurements is illustrated in Table I.

In early pregnancy, these fetal limb bones are comprised of a primary ossification center (calcified) plus proximal and distal cartilaginous structures. The roent-genologic examination shows only the ossification center. It appears that ultrasound fetal limb bone lengths correspond to the ossification centers as seen on x-ray films

A subsequent eight cases confirmed the correlation of measurements of the fetal femur by ultrasound and x-ray examination. Generally, the ultrasound measurement was 1 to 2 mm greater than the x-ray one, perhaps because of beam-width effect and lateral loss of resolution.

#### Results

The measurements of the various limbs grouped according to weeks of gestation are presented in Tables II to V. The weeks of gestation indicate weeks completed from the first day of the last normal menstrual period. The data are presented as the arithmetic mean  $\pm$  2 standard deviations. The number of determinations for each week of gestation is also presented.

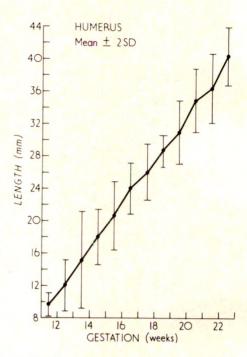


Fig. 4. Length of humerus plotted against weeks of gestation.

As illustrated in Figs. 3 through 6, it appears that the growth of all of the limb bones was linear from 12 weeks' gestation. The different measurements of limb bone length had similar growth curves. The femur had the largest weekly increments (approximately 3 mm per week), and the tibia-fibula had the smallest at 2.5 mm per week. Measurements of the femur had generally the smallest weekly standard deviation, which thus reflects the greater ease of measurement and the better reproducibility.

#### Comment

In 1929, Scammon and Calkins<sup>4</sup> published postmortem data after measuring limbs of fetuses between 8 weeks and term. Mahoney and Hobbins<sup>5</sup> reported data for full arm and leg lengths determined on 22 aborted fetuses. Both of these studies provided data on external measurements, which included bone and soft tissue. To date, there is little information in regard to fetal limb bone lengths in early gestation. The present study establishes ultrasound measurements specifically for fetal limb bone lengths.

The measurements  $\pm 2$  SD have been determined for the bone lengths of the fetal limbs. These measurements represent the bone lengths for 95% of the normal population and provide the means to study patients who are at risk for skeletal dysplasias.

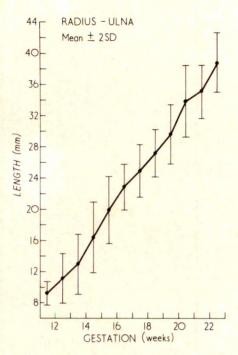


Fig. 5. Length of radius-ulna complex plotted against weeks of gestation.

Patients who have a history of a child affected with a specific skeletal dysplasia or multiple congenital malformations can be screened during the second trimester. If a skeletal abnormality is present, it may be detected early enough for termination of pregnancy, if desired. If no skeletal abnormality is present, serial determinations of the fetal limb lengths will monitor the growth of the limbs in order to assure normal development.

Subsequent to this study, three patients were examined who were at risk for skeletal dysplasias. In two, the fetuses had normal long bone measurements up to 24 weeks' gestation and were allowed to continue to term. At delivery, the babies were found to have normal limb lengths. The third patient was diagnosed as having a fetus with a limb-reduction deformity. She was a 28year-old Caucasian, gravida 2, para 1, whose first child was a diastrophic dwarf. She was referred for ultrasound examination at a menstrual age of 13 weeks and 5 days. The crown-rump length was 43 mm, which corresponded to a gestational age of 11 weeks. Three weeks later, an ultrasound examination of the fetal limbs was performed. The difficulty in adequately outlining the limbs at this gestational age suggested an abnormality. A femur length of 9 mm was recorded (normal range, 13 to 20 mm).

At 16 weeks' gestation it was possible to obtain a re-

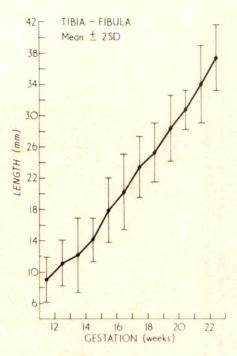


Fig. 6. Length of tibia-fibula complex plotted against weeks of gestation.

producible femur length measurement of 13 mm (normal range, 19 to 26 mm). This was well below the expected range for the period of gestation. A diagnosis of dwarfism was made on the basis of markedly shortened femur measurements. Because diastrophic dwarfism syndrome includes varus clubfoot, micrognathia, and cleft palate, fetoscopy was used to determine the degree of fetal malformation. It revealed that the limbs were abnormally short and curved. Fetal features were consistent with a diagnosis of diastrophic dwarfism.

After discussion with the patient, the pregnancy was terminated; postmortem examination confirmed the gross shortening of the long bones, varus deformities, micrognathia, and cleft palate.3

Since the length of the femur can be determined easily, and since the physiologic variation is relatively small, it may be helpful in establishing the correct gestational age. The growth of the femur is linear from 12 to 22 weeks. It may be used as an alternative to or in conjunction with the present parameters measured by ultrasound.

We wish to express our thanks to the Department of Radiology, and to Dr. Driver for pathologic review.

#### REFERENCES

- 1. Reinold, E.: Ultrasonics in early pregnancy; diagnostic scanning and fetal motor activity, Basel, 1976, Karger.
- 2. O'Brien, G. D., Queenan, J. T., and Campbell, S. P.: Real time ultrasound measurement of the femur length in the assessment of gestational age. In preparation.
- 3. O'Brien, G. D., Rodeck, C., and Queenan, J. T.: Early prenatal diagnosis of diastrophic dwarfism by ultrasound, Br. Med. J. **280**:1300, 1980.
- 4. Scammon, R. E., and Calkins, L. A.: Development and growth of the human body in the fetal period, Minneapolis, 1929, University of Minnesota Press.
- Mahoney, M. J., and Hobbins, J. D.: Prenatal diagnosis of chondroectodermal dysplasia (Ellis-van Creveld syndrome) with fetoscopy and ultrasound, N. Engl. J. Med. 297:258, 1977.

#### Copyright information

The appearance of a code at the bottom of the first page of an original article in this JOURNAL indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc., 21 Congress St., Salem, Mass. 01970, (617)744-3350, for copying beyond that permitted by Section 107 or 108 of the U. S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale. For reprint quantities of 50 or more, please contact Publisher.

### Possible acceleration of neurological maturation following high-risk pregnancy

CLAUDINE AMIEL-TISON

Paris, France

Evidence of an advance in neurological maturation of 4 weeks or more was detected in 16 infants with gestational ages between 30 and 37 weeks. These infants were all from pregnancies in which it is fair to conclude that one form or another of intrauterine stress was in operation. The hypothesis is advanced that unfavorable intrauterine conditions can induce an acceleration of neurologic development. (AM. J. OBSTET. GYNECOL. 138:303, 1980.)

SINCE BUDIN first noted the wide-awake, hyperactive behavior of the small-for-date infant, the idea that unfavorable intrauterine conditions may accelerate the development of the infant's central nervous system has been publicized.

This idea was first supported by the observation that experimentally produced small-for-dates rats opened their eyes 24 hours earlier than control rats.<sup>1</sup> Then Gould and associates<sup>2</sup> first reported clinical evidence of accelerated neurological maturation induced by intrauterine stress. This paper reports the details of 16 infants, identified in the course of a routine practice, in whom the neurological age was 4 weeks or more in advance of gestational age (as estimated from the mother's last menstrual period).

Since an advance of 4 weeks is probably outside the 95% confidence limits of an estimate based on a neurological examination,<sup>3</sup> it constitutes evidence in support of the hypothesis that advanced neurological maturation can occur.

#### Patients and methods

The 16 cases were selected from 1,400 infants of gestations between 30 and 37 weeks, admitted to the neonatal department between 1972 and 1978. The

From the Department of Pediatrics, Port-Royal Maternity Hospital.

Supported by National Institute of Health and Medical Research Grant INSERM No. 56,7888.

Received for publication December 3, 1979.

Revised May 27, 1980.

Accepted June 4, 1980.

Reprint requests: Claudine Amiel-Tison, M.D., Department of Pediatrics, Port-Royal Maternity Hospital, 123 Boulevard de Port-Royal, 75014 Paris, France. upper limit of 37 weeks was chosen because estimation of gestation by the neurological method becomes very uncertain at 38 weeks and above. Cases were reselected only when the mother could provide a precise menstrual history which corresponded to the obstetrician's clinical examination of the mother. Details of antenatal history were obtained from the obstetrician's record. Maternal hypertension was defined as a diastolic pressure equal to or greater than 90 mm Hg on two or more occasions. The small-for-date infant was defined as having a birth weight below the tenth percentile of Lubchenco's<sup>4</sup> intrauterine growth curve. Neurological maturation was assessed by a method previously described. 5-8 This method gives an estimate of neurological age within a 2-week interval for 16 separate tests. All infants were examined on the first and third days of life. Cases were selected only when all 16 tests were within the same 2-week intervals on both days.

#### Results

Table I gives details of findings in the 16 infants. The estimated advance in neurological development was between 4 and 7 weeks.

Hypertension was noted in seven mothers. Four mothers had chronic hypertensive disease, and three had pregnancy-induced hypertension. Three mothers had uterine malformations. Glucocorticoids had been given in four cases to accelerate fetal lung development. Three mothers had twins, and three had triplets. Ovulation had been stimulated pharmacologically in five of the six multiple pregnancies.

All infants survived. Only three infants one of them a triplet, were small for dates. Nine of the infants had a satisfactory neonatal course with only transient respiratory distress in four of them. The remaining seven showed a range of illnesses frequently encountered in

Table I. Details of 16 cases of accelerated neurological maturation

Case No.	Sex	Birth weight (gm)	Length (cm)	Head circumference (cm)	Gestational age (wk)	Neurological age (wk)	Gestational history
1	F	1,520	42	29	30	34	Uterine malformation
2	M	1,990	47	32	33	37-38	Permanent hypertension (previous stillbirth)
3	M	2,130	46	30	33	37-38	Twin pregnancy, pre-eclamptic toxemia
4	F	1,000	37	29	34	38	Permanent hypertension
5	F	1,340	40	28	34	38	Pre-eclamptic toxemia
6	M	1,150	37	28	30	36)	Triplet pregnancy, ovulation stim-
7	M	1,330	42	29	30	34	ulated
8	M	1,500	42	29	30	34	
9	M	1,460	39	27	28	35-36	Vaginal bleeding, repeated false labor, prenatal glucocorticoids
10	M	1,460	41	28	31	35-36	Pre-eclamptic toxemia
11	M	1,180	38	26	28	32	Repeated false labor
12	F	2,000	45	31	34	38	Permanent hypertension
13	M	2,360	48	34	36	40	Diabetes—Class D, permanent hypertension
14	M	1,500	43	28	31	35-36	Uterine malformation, premature rup- mature rupture of membrane for 6 days, prenatal glucocorticoids
15	F	1,830	42	31	33	38)	Uterine malformation, ovulation stim-
16	M	1,600	42	28	33	38	ulated, twin pregnancy, premature rupture of membranes for 7 days, prenatal glucocorticoids

<sup>\*</sup>Below Lubchenco's tenth percentile.

any group of low-birth weight infants. One had a subarachnoid hemorrhage and apneic spells but was normal at follow-up. One required mechanical ventilation for severe respiratory distress syndrome. Two had enterocolitis. One had low Apgar scores and later developed signs of a patent ductus arteriosus. One developed hyperexcitability which persisted at 5 months of age. One had an exchange transfusion as treatment for a high hematocrit.

#### Comment

A clinical study such as this one meets with three major difficulties. (1) The normal variation in the result of a neurological examination is considerable, according to Finnström.<sup>3</sup> The 95% confidence limit for a neurological estimate of gestation is ±23.4 days. (2) Unfavorable intrauterine conditions are hard to identify and impossible at present to quantify. (3) A reliable estimate

of gestational age is not always available and, however obtained, is also subject to natural variation.

Since only 1% of the babies of gestational ages between 28 and 37 weeks showed definite evidence of advanced neurological development, we cannot rule out the possibility that they represent the extreme upper end of a normal distribution. However, since we selected only cases in which we felt very confident in the diagnosis, the 1% was almost certainly an underestimate of the true incidence.

Futhermore, we can reasonably assume that the 95% confidence limit of ±23 days reported by Finnström³ has been reduced in this particular study since all newborn infants were evaluated by the same observer, ruling out the usually poor reproducibility of this type of clinical evaluation. Therefore, only two factors must be considered: First, the error of estimating the gestational age from the last menstrual period is at best ±1

Intrauterine growth retardation*	Neonatal course	Follow-up					
0	Arachnoid hemor- rhage, apneic spells	Normal at 2 yr					
0	Normal	No information					
0	Exchange transfusion for high hematocrit	No information					
+	Normal	Normal at 4 mo					
+	Normal	No information					
+	Normal	Normal at 4 mo					
0	Transitory respiratory distress syndrome	Normal at 4 mo					
0	Severe respiratory distress syndrome, artificial ventilation	Normal at 4 mo					
0	Hyperexcitability	Persisting hyper- excitability at 5 mo					
0	Transitory respiratory distress syndrome	No information					
0	Low Apgar score, pa- tent ductus arterio- sus	Normal at 5 mo					
0	Necrotizing entero- colitis	Normal at 3 mo					
0	Low Apgar score, transitory respira- tory distress syn- drome, mild abnor- mal neurological signs	Normal at 11 mo					
0	Transitory respiratory distress syndrome	Normal at 9 mo					
0	Normal	Normal at 6 mo					
0	Necrotizing entero- colitis	Normal at 6 mo					

week; second, although not known, the biological variations are probably at least ±1 week.

To demonstrate that maturation is advanced by intrauterine stress, it would be necessary first to select a group of pregnancies in which the unfavorable intrauterine conditions were objectively identified and second to show a significant increase of advanced neurological maturation compared to a control group. This kind of proof is not available at present, but details of the pregnancies listed in Table I do provide some qualitative support for the hypothesis.

In each case there was evidence of some unfavorable intrauterine factor such as chronic hypertensive disease, pregnancy-induced hypertension, uterine malformation, or multiple pregnancy. The incidence of hypertension found in seven of the 16 pregnancies (47%) is much higher than the incidence of hypertension found (according to a similar definition) in 52 of 352 pregnancies (14%) resulting in premature delivery between 28 and 37 weeks during the 2-year period of 1976 to 1978.

We can only speculate on whether or not the steroids given to four of the 16 mothers contributed to an advance in maturation.

As mentioned in the introduction, accelerated neurological development has been produced in rats subjected to intrauterine malnutrition by restriction of vascular supply to the uterus.4 More recent experiments have shown a more rapid turnover of tryptophan and serotonin in the brains of undergrown rats than in the brains of normal rats.9 This may well be relevant since serotonin appears to play a role in the maturation of the nervous system of several species. 10-12

The influence of unfavorable intrauterine conditions in accelerated maturation may not be confined to the central nervous system. Gould and associates13 reported an advance in both pulmonary surfactant and neurological development in eight of 51 infants from high-risk pregnancies. They also reported that 25 infants with accelerated surfactant development also had signs of neurological advancement.

Finally we may speculate whether corticosteroid secretion by the fetus, in response to stress may play a role in the induction of these effects. Liggins and Howie<sup>14</sup> have demonstrated an accelerating effect of glucocorticoids on lung development and De Lemos<sup>15</sup> reported a parallel advance in maturation of both the lung and the brain following experimental injection of glucocorticoids into the fetus.

#### REFERENCES

- 1. Chanez-Bel, C.: Personal communication. Centre de recherches neonatales, Port-Royal Hospital.
- 2. Gould, J. B., Gluck, L., and Kulovich, M. V.: The acceleration of neurological maturation in high stress pregnancy and its relation to fetal lung maturity, Pediatr. Res. 6:276, 1972
- Finnström, O.: Studies on maturity in newborn infants. VI. Comparison between different methods for maturity estimation, Acta Paediatr. Scand. 61:33, 1972.
- 4. Lubchenco, L., Hansman, C., Dressler, M., et al: Intra-
- uterine growth as estimated from live-born birth weight data at 24 to 42 weeks of gestation, Pediatrics 32:793,
- 5. Amiel-Tison, C.: Neurological evaluation of the maturity of newborn infants, Arch. Dis. Child. 43:89, 1968.
- 6. Amiel-Tison, C.: Neurological evaluation of the small neonate: the importance of head straightening reactions, in Gluck, L., editor: Modern Perinatal Medicine, Chicago, 1974, Year Book Medical Publishers, Inc., p. 347.
- 7. Thomas, A., and Saint Anne Dargassies, S.: Etudes neu-

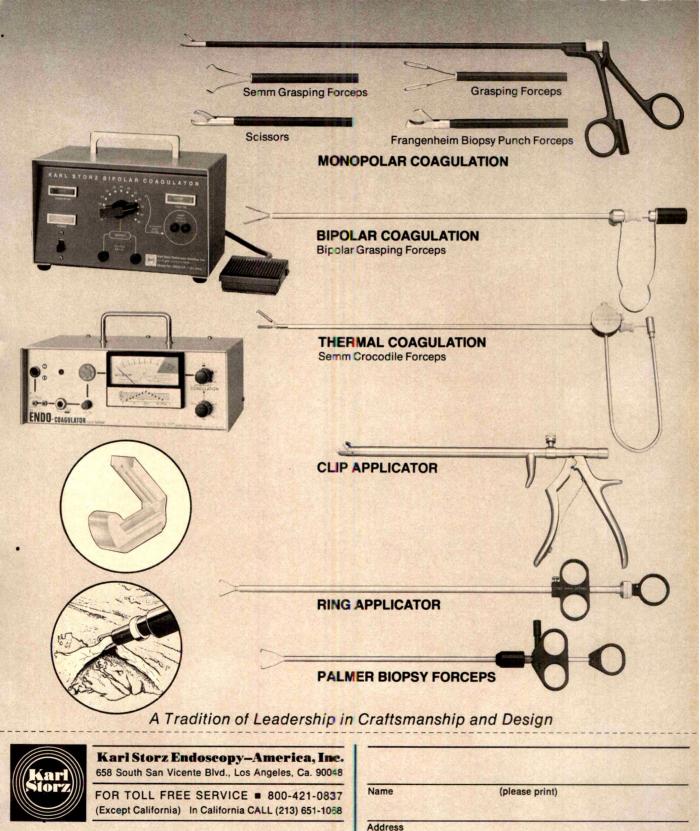
- rogiques sur le nouveau-ne et le jeune nourrisson, Paris, 1952, Masson & Cie.
- 8. Saint Anne Dargassies, S.: La maturation neurologique du prematuré. Etudes Neonatal. 4:71, 1955.
- 9. Chanez-Bel, C., et al.: In preparation.
- Baker, P. C., and Quay, W. B.: 5-Hydroxytryptamine metabolism in early embryogenesis and the development of brain and retinal tissues. A review, Brain Res. 12:273, 1969.
- Hole, K.: Reduced 5-hydroxyindole synthesis reduces postnatal brain growth in rats, Eur. J. Pharmacol. 18:361, 1972.
- 12. Lauder, J. M., and Krebs, H.: Effects of p-chlorophenylalanine on time of neuronal origin during embryogenesis in the rat, Brain Res. 107:638, 1976.
- Gould, J. B., Gluck, L., and Kulovich, M. V.: The relationship between accelerated pulmonary maturity and accelerated neurological maturity in certain chronically stressed pregnancies, Am. J. Obstet. Gynecol. 127:181, 1977.
- 14. Liggins, G., and Howie, R.: A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants, Pediatrics 50:515, 1972.
- De Lemos, R. A.: Glucocorticoid effect: organ development in monkeys, in Moore, T. D., editor: Lung Maturation and the Prevention of Hyaline Membrane Disease, Report of the Seventieth Ross Conference on Pediatric Research, Columbus, Ohio, 1975, Ross Laboratories, p. 77.

#### Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following written statement, signed by one author: "The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C. V. Mosby Company in the event the work is published. The undersigned author warrants that the article is original, is not under consideration by another journal, and has not been previously published. I sign for and accept responsibility for releasing this material on behalf of any and all co-authors." Authors will be consulted, when possible, regarding republication of their material.

## IT'S YOUR CHOICE

for Tubal Sterilization from Karl Storz



City

Gentlemen:

☐ Please send me further information. ☐ Please have a

#### Articles to appear in early issues

#### Malacoplakia of the female genital tract

A. Chalvardjian, B.A., M.D., F.R.C.P.(C.), L. Picard, M.D., R. Shaw, M.D., F.R.C.P.(C.), R. Davey, M.D., F.R.C.S.(C.), and J. D. Cairns, M.A., F.A.C.S., F.R.C.S.(C.)

Toronto, Ontario, Canada

#### Response to repetitive luteinizing hormone-releasing hormone stimulation in hypothalamic and pituitary disease

Anne Colston Wentz, M.D., and Richard N. Andersen, Ph.D. Memphis, Tennessee

#### The effect of radical hysterectomy on bladder physiology

J. Peter Forney, M.D. Dallas, Texas

#### The standing cystometrogram

Stuart A. Weprin, M.D., and Frederick P. Zuspan, M.D., F.A.C.O.G. Columbus, Ohio

#### Maternofetal electrical potential difference in conscious sheep: Effect of fetal death or acidosis

A. P. Weedon, T. E. Stacey, Jane F. Canning, R. H. T. Ward, and R. D. H. Boyd London, England

#### Placental size during early pregnancy and fetal outcome: A preliminary report of a sequential ultrasonographic study

Henk J. Hoogland, M.D., Jelte de Haan, M.D., and Chester B. Martin, Jr., M.D. Nijmegen, The Netherlands

#### Nonstressed antepartum heart rate monitoring: Implications of decelerations after spontaneous contractions

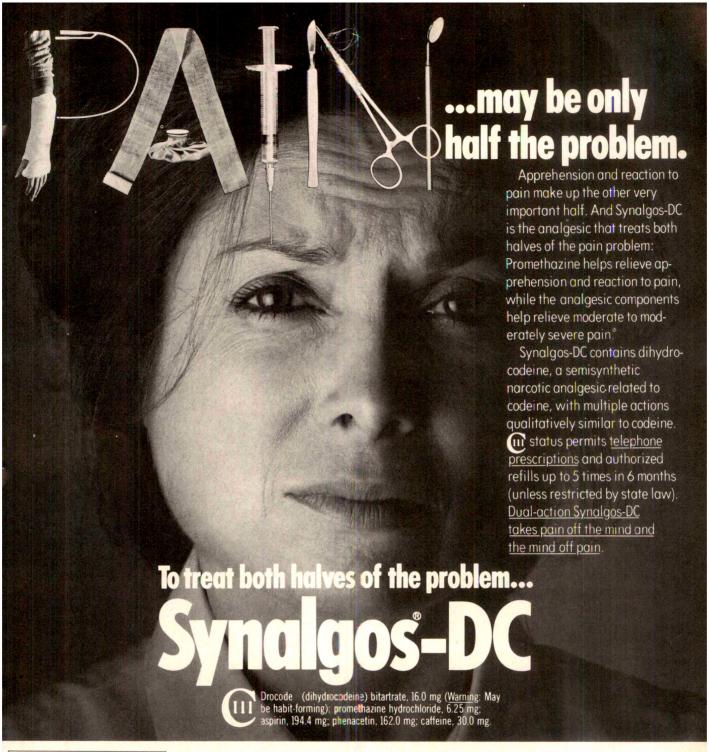
G. H. A. Visser, C. W. G. Redman, H. J. Huisjes, and A. C. Turnbull Oxford, England, and Groningen, The Netherlands

#### Blind oxytocin challenge test and perinatal outcome

K. J. Staisch, M.D., J. R. Westlake, Ph.D., and R. A. Bashore, M.D. Los Angeles, California

#### Postpartum lymphocytic thyroiditis in American women: A spectrum of thyroid dysfunction

Henry G. Fein, M.D., Joel M. Goldman, M.D., and Bruce D. Weintraub, M.D. Bethesda, Maryland



\*INDICATIONS: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective for the relief of moderate to moderately severe pain in those situations where the physician wishes to add a mild sedative effect. Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Hypersensitivity to dihydrocodeine, promethazine, aspirin, phenacetin. WARNINGS: Salicylates should be used with extreme caution in the presence of peptic ulcer or coagulation abnormalities.

Drug Dependence: Dihydrocodeine can produce drug dependence of the codeine type and therefore has the potential of being abused. Psychic dependence, physical dependence and tolerance may develop upon reneated administration of dihydrocodeine

and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, dihydrocodeine is subject to the provisions of the Federal Controlled Substances Act. Usage in Ambulatory Patients: Dihydrocodeine and promethazine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Synalgos-DC should be cautioned accordingly. Interactions with other Central Nervous System Depressants: Patients receiving other narcotic analgesics, general anesthetics, other phenothiazines, tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Synalgos-DC may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Patients who have demonstrated a hypersen

sitivity reaction (e.g. blood dyscrasia, jauncice) with a phenothiazine should not be reexposed to any phenothiazine, including Synalgos-DC, unless in the judgment of the physician the potential benefits of the treatment outweigh the possible hazards. Usage in Pregnancy: Reproduction studies have not been performed in animals. There is no adequate information on whether this drug may affect fertility in human males and females or has a teratogenic potential or other adverse effect on the fetus. Usage in Children: Since there is no experience in children who have received this drug, safety and efficacy in children have not been established.

PRECAUTIONS: Phenacetin has been reported to damage kidneys when taken in large amounts for a long time. Promethazine should be administered cautiously to patients with cardiovascular or liver disease. Synalgos-DC should be given with caution to certain patients such as the elderly or debilitated, and those with hypothyraidism. Addison's disease and

prostatic hypertrophy and urethral stricture.

ADVERSE REACTIONS: The most frequently observed reactions include lightheadedness, dizziness, drowsiness, sedation, nausea, vomiting, constipation, pruritus, skin reactions, and constipation, pruritus, skin reactions, and

rarely, hypotension.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. Synalgos-DC is given orally. The usual adult dose is 2 capsules every 4 hours as needed for pain. DRUG INTERACTIONS: The CNS depressant effects of Synalgos-DC may be additive with that of other CNS depressants. See Warnings. Aspirin may enhance the effects of anticoagulants and inhibit the uricosuric effects of uricosuric agents.

Consult direction circular before prescribing.

IVES LABORATORIES INC. New York, NY 10017

Dedicated to improving the



## Amouncing-

US AND NEONATE

New 4th Edition!
DIAGNOSIS AND
MANAGEMENT OF
THE FETUS AND
NEONATE AT
RISK: A Guide for
Team Care
By S. Gorham
Babson, M.D.; Martin
L. Pernoll, M.D.; and
Gerda I. Benda; with
the assistance of
Katherine Simpson,
R.N.

This successful new edition:

details information needed to identify and manage the high-risk mother, fetus, and infant

 offers new chapters on multiple pregnancy, very low birth weight infants, and parenteral administrations of fluids and electrolytes

October, 1979. 358 pages, 99 illustrations. Price, \$21.95.

New 2nd Edition!
CLINICAL PERINATOLOGY

Edited by Silvio Aladjem, M.D.; Audrey K. Brown, M.D.; and Claude Sureau, M.D.; with 45 contributors.

"Brings together skillfully and thoroughly those clinical concepts dedicated to enhancing the unborn's quality of life and ultimately the quality of life of the newborn."

Modern Medicine review of the first edition

December, 1979. 638 pages, 286 illustrations. Price, \$49.50.



THE C. V. MOSBY COMPANY 11830 WESTLINE INDUSTRIAL DRIVE ST. LOUIS, MISSOURI 63141

A New Book!

REAL TIME ULTRASOUND IN OBSTETRICS

Edited by M.J. Bennett, M.D., M.R.C.O.G., and S. Campbell, M.B., B.S., F.R.C.O.G.; with 15 contributors. This outstanding reference:

- provides an in-depth look at the use of ultrasound in obstetrics
- describes the role of real time both clinically and as a complementary procedure and details specific applications of the technique

September, 1980. Approx. 160 pages, 88 illustrations. About \$35.00.

To order your 30-day on-approval copies, CALL US! Dial toll-free (800) 325-4177, ext. 10. In Missouri, call collect (314) 872-8370, ext. 10 during our regular business hours.

MasterCard, VISA, or C.O.D. accepted.

All prices subject to change

A New Book! **ESSENTIAL REPRODUCTION.** By Martin H. Johnson, M.A., Ph.D. and Barry J. Everitt, M.A., Ph.D.

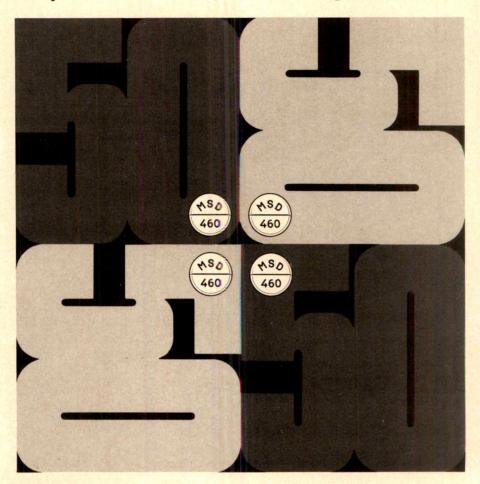
- provides an integrated approach to the study of reproduction
- covers anatomical, physiological, genetic, biochemical, and behavioral aspects

September, 1980. Approx. 358 pages, 137 illustrations. About \$17.75.

New 4th Edition! LECTURE NOTES ON GYNAECOLOGY. By Josephine Barnes, D.B.E., M.A., D.M., F.R.C.P., F.R.C.S., F.R.C.O.G., Hon.F.R.C.P.I. May, 1980. 219 pages, 26 illustrations. Price, \$12.95.

New 4th Edition! LECTURE NOTES ON OBSTETRICS. By G.V.P. Chamberlain, M.D., F.R.C.S.,

for neurogenic atony of the urinary bladder with retention, higher titrated dosages may be needed (up to 200 mg/day)



# **MSD** announces

(BETHANECHOL CHLORIDE | MSD)

when higher titrated dosages are indicated

After titration, dosages as high as 50 mg t.i.d. or q.i.d. have been effectively employed in neurogenic atony of the urinary bladder as well as for the treatment of postoperative and postpartum nonobstructive (functional) urinary retention.

- Helps to initiate micturition and empty the bladder.
- Helps to reduce the frequency of bladder catheterization

Contraindicated in hypersensitivity to

URECHOLINE, hyperthyroidism, pregnancy, peptic ulcer, latent or active bronchial asthma, pronounced bradycardia or hypotension, vasomotor instability, coronary artery disease, epilepsy, and parkinsonism.

URECHOLINE should not be used when the strength or integrity of the gastrointestinal or bladder wall is in question or in the presence of mechanical obstruction. If necessary, the effects of the drug can be. abolished promptly by atropine.

for neurogenic atony of the urinary bladder with retention, higher titrated dosages may be needed (up to 200 mg/day)

# 50-mg URECHOLINE® (BETHANECHOL CHLORIDE | MSD)



Contraindications: Hypersensitivity to Tablets URECHOLINE (Bethanechol Chloride, MSD) or to any component of Injection URECHOLINE; hyperthyroidism, pregnancy, peptic ulcer, latent or active bronchial asthma, pronounced bradycardia or hypotension, vasomotor instability, coronary artery disease, epilepsy, and parkinsonism. Should not be employed when the strength or integrity of the gastrointestinal or bladder wall is in question, or in the presence of mechanical obstruction; when increased muscular activity of the gastrointestinal tract or urinary bladder might prove harmful, as following recent urinary bladder surgery, gastrointestinal resection and anastomosis, or when there is possible gastrointestinal obstruction; in bladder neck obstruction, spastic gastrointestinal disturbances, acute inflammatory lesions of the gastrointestinal tract, or peritonitis; or in marked vagotonia.

Warnings: The sterile solution is for subcutaneous use only. It should never be given intramuscularly or intravenously. Violent symptoms of cholinergic overstimulation, such as circulatory collapse, fall in blood pressure, abdominal cramps, bloody diarrhea, shock, or sudden cardiac arrest are likely to occur if the drug is given by either of these routes. Although rare, these same symptoms have occurred after subcutaneous injection, and may occur in cases of hypersensitivity or overdosage.

**Precautions:** Special care is required in patients receiving ganglion blocking compounds because a critical fall in blood pressure may occur; usually, severe abdominal symptoms appear before there is such a fall in blood pressure. In urinary retention, if the sphincter fails to relax as the drug contracts the

bladder, urine may be forced up the ureter into the kidney pelvis; if there is bacteriuria, this may cause reflux infection.

Adverse Reactions: Abdominal discomfort, salivation, flushing of the skin ("hot feeling"), sweating. Large doses more commonly result in effects of parasympathetic stimulation, such as malaise, headache, sensation of heat about the face, flushing, colicky pain, diarrhea, nausea and belching, abdominal cramps, borborygmi, asthmatic attacks, and fall in blood pressure.

Atropine is a specific antidote. The recommended dose for adults is 0.6 mg (1/100 grain). The recommended dosage in infants and children up to 12 years of age is 0.01 mg/kg repeated every two hours as needed until the desired effect is obtained, or adverse effects of atropine preclude further usage. The maximum single dose should not exceed 0.4 mg. Subcutaneous injection of atropine is preferred except in emergencies when the intravenous route may be employed. When Injection URECHOLINE is used, a syringe of atropine sulfate should always be available.

How Supplied: Tablets, containing 5 mg, 10 mg, 25 mg, or 50 mg bethanechol chloride each, in bottles of 100 and single-unit packages of 100; Injection, 5 mg per ml, is a clear, colorless solution, and is supplied in boxes of 6 × 1-ml vials.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, PA 19486

MERCK SHARP DOHME

#### GYNECOLOGY

Technical failures in tubal ring sterilization: Incidence, perceived reasons, outcome, and risk factors

I-CHENG CHI, M.D., DR.P.H.
STEPHEN D. MUMFORD, DR.P.H.
LEONARD E. LAUFE, M.D.
Research Triangle Park, North Carolina

Six centers participated in comparative studies of female sterilization conducted by the International Fertility Research Program. The incidence of technical tailures (or failed attempts) was compared between patients sterilized with the tubal ring and those sterilized with other tubal occlusion techniques. The tubal ring was associated with a higher failure rate than electrocoagulation, the Rocket clip, or the modified Pomeroy technique. Of 1,035 tubal ring sterilizations, there were 38 technical failures. Reasons given by the operators for the failures, by frequency of occurrence, were surgical complications, conditions preexisting in the patients, and problems with the instruments. Most of these failures were remedied by changing to other techniques. In two patients, the procedure was completed by changing the approach from laparoscopy to laparotomy. In five others, sterilization was not completed. Case-control analysis was performed and three risk factors were delineated: obesity, prior use of an intrauterine contraceptive device and previous abdominal operations. (Am. J. Obstet. Gynecol. 138:307, 1980.)

INCREASED acceptance of female sterilization for contraceptive purposes during the last decade<sup>1</sup> can be partly attributed to the acceptance of the laparoscope, the widespread use of minilaparotomy, and the development of new tubal occlusion techniques. The safety and efficacy of these new techniques have been examined extensively, but the problem of technical failures, frequently referred to as failed attempts, has often

From the International Fertility Research Program.

Received for publication March 11, 1980.

Revised May 15, 1980.

Accepted May 19, 1980.

Retript requests: Lehma Chi, M.D., International

Reprint requests: I-cheng Chi, M.D., International Fertility Research Program, Research Triangle Park, North Carolina 27709.

been ignored, in spite of its important bearing on satisfaction of the patient and efficiency of the program. Furthermore, exclusion of patients with technical failures from these analyses has resulted in an underestimated rate of complications and a distorted picture of the benefit/risk ratio of a sterilization technique.

Use of the tubal ring for sterilization is safer than electrocoagulation, <sup>1, 2</sup> and is more effective in preventing poststerilization pregnancies than the other mechanical devices, namely, the prototype spring-loaded clip and the tantalum clip. <sup>3, 4</sup> This study compares the incidence of technical failures in patients sterilized with the tubal ring with that of failures in patients sterilized by other techniques. It also examines the natural history of the ring failures with regard to the operators' perceived reasons for failure, management, outcome, and risk factors.

**Table I.** Incidences of technical failures in tubal ring and other tubal occlusion techniques, by center and surgical approach

		Companytive tobal		Technical failures	
Center	Surgical approach	Comparative tubal occlusion techniques	No. of patients	No.	Rate (%)
A	Laparoscopy	Tubal ring	131	10	7.6
	,	Electrocoagulation (p < 0.01 by Fisher's exact test)	126	0	0.0
В	Laparoscopy	Tubal ring	150	2	1.3
	• • •	Electrocoagulation (N5*)	150	0	0.0
C†	Laparoscopy	Tubal ring	300	2 3	0.7
	,	Prototype spring-loaded clip (NS*)	300	3	1.0
D‡	Laparoscopy	Tubal ring	96	9	9.4
	,	Rocket clip (p < 0.01 by Fisher's exact test)	96	0	0.0
E	Culdoscopy	Tubal ring	109	3	2.8
	1,	Tantalum clip (NS*)	113	1	0.9
F	Minilaparotomy	Tubal ring	249	12	4.8
	*	Modified Pomeroy $(p < 0.01 \text{ by } \chi^2 \text{ test})$	250	4	1.6

<sup>\*</sup>NS = Not significant.

**Table II.** Reported reasons for technical failures in patients undergoing tubal ring sterilization

Reason	No. of patients
Surgical complications	
Transected tube(s)*	15
Mesosalpingian bleeding	. 1
Severe pain	1
Subtotal	17 (44.7%)
Preexisting conditions	
Pelvic adhesions	9
Thick tube or hydrosalpinx	4
Subtotal	13 (34.2%)
Instrument problems	, ,
Trocar too short to reach the peritoneal cavity	4
Failure of ring applicator	2
Unspecified	2
Subtotal	8 (21.1%)
Total	38 (100%)

<sup>\*</sup>Three with hematoma.

#### Material and methods

In June, 1975, the International Fertility Research Program (IFRP) started to coordinate comparative female sterilization studies among its network of contributing physicians. To qualify for participation, the physicians must have demonstrated similar competency in both tubal occlusion techniques to be compared and must have agreed to comply with the following protocol requirements: (a) patients voluntarily requesting female sterilization for contraceptive purposes were to be randomly allocated to one of the two techniques; (b) the

**Table III.** Outcome in patients undergoing tubal ring sterilization, with and without technical failures

	With technical failures (N = 38)	Without technical failures (N = 997)
% With surgical difficulties	73.7	10.2
% With surgical complications	50.0	1.7
Length of operation (in minutes)	$15.3 \pm 1.10*$	$8.4 \pm 0.14*$
% Hospitalized for 1 or more days after sterilization procedure	39.5	28.3
% With early complications	9.1	20.0

<sup>\*</sup>Mean time ± standard error.

patients were to receive follow-up care, with their complications and complaints recorded by a physician who was unaware of the technique used; (c) all the collateral procedures (e.g., type of anesthesia, preoperative medication, and surgical approach) were to be the same for the two groups of patients; (d) all contributing physicians were to use the same standardized form for recording data and the same definitions of terms. Although there was to be only one operator in each center, this requirement was not strictly enforced because of practical difficulties.

Previous abdominal and/or pelvic operations and moderate obesity were not considered to be contraindications for sterilization.

By January, 1978, six centers had completed a comparative study in which the tubal ring was one of the

<sup>†</sup>In this center, postabortion and postpartum patients were studied.

<sup>‡</sup>In this center, double-puncture laparoscopy was the approach used.

**Table IV.** Risk factors associated with technical failures by reported reasons in patients undergoing tubal ring sterilization\*

			Reasons for te	c¹nica! failure		·		
	Surgical co	omplications	Preexistin	g conditions	Instrum	ent problems	T	otal
Risk factor	Cases (N = 15)	$\begin{array}{c} Controls\\ (N=30) \end{array}$	Cases (N = 13)	Centrols $(N = 26)$	Cases (N = 8)	Controls $(N = 16)$	Cases (N = 36)	$\begin{array}{c} Controls\\ (N=72) \end{array}$
Obesity†					•			
No. of patients	0	1	4	2	4	0	8	3
% of patients	0.0	3.3	30.8	7.7	50.0	0.0	22.2	4.2
χ² value	(	0.50	•	2.08		8.00		5.45
p value	N	IS‡	N	/S\$	<	0.01	< 0.05	
Odds ratios	•	_		- '		∞	•	7.50
Prior IUD use								
No. of patients	7	6	5 .	2	3	· 2	15	10
% of patients	46.7	20.0	<b>38.5</b> .	2 7.7	37.5	12.5	· 41.7	13.9
$\chi^2$ value		4.57		5.53		2.00	1	1.76
p value	<(	0.05	. <	0.05	ì	NS‡	<	0.01
Odds ratios	` :	5.00		9.00	-	_		6.00
Previous abdominal operations		_			•	•		
No. of patients	2	3	5	-1	0 .	0	7	4
% of patients	13.3	10.0	38.5	3.8	0.0	0.0	19.4	5.6
χ² value	. (	0.10		6.75		0.00		4.55
p value	N	S‡	<	0.01	1	NS‡		0.05
Odds ratio		<u>-</u> ' ,		0.00				3.50

<sup>\*</sup> $\chi^2$  value and odds ratios were calculated by matched triplet analysis.<sup>5</sup> This table, however, is presented in the usual manner for simplicity and clarity.

two techniques used. Four centers were in Asia, and one each was in the Middle East and Europe. In five centers, only interval patients whose last pregnancies had terminated at least 42 days prior to sterilization were studied. In the other center, Center C, postabortion and postpartum patients were studied. The surgical approaches were single-puncture laparoscopy (three centers), double-puncture laparoscopy (one center), culdoscopy (one center), and minilaparotomy (one center). Tubal occlusion techniques compared with the tubal ring were electrocoagulation, the prototype spring-loaded clip, the Rocket clip, the tantalum clip, and the modified Pomeroy technique (Table I). The mean age of the patients was 32.5 years, and their mean parity was 4.7.

A technical failure was defined as a sterilization procedure that was uncompleted or that was completed by changing to a tubal occlusion technique or surgical approach other than the one originally planned.

Patients sterilized with the tubal ring and patients sterilized by other techniques were compared within each center with respect to the incidences of technical failures. Either the chi-square test or Fisher's exact test was used for statistical evaluation; differences with a p value of <0.05 were considered to be statistically significant. Analysis was then confined to tubal ring pa-

tients only. Technical failures were examined for perceived reasons and management of the failures by the operators. Patients with and those without technical failure were then compared by outcome. Finally, the risk factors associated with tubal ring failures were de--lineated by a case-control analysis in which a case (patient with technical failure) was individually matched with two controls (patients without technical failure) by age (within 5 years), center, operator, and date of operation (one control was selected immediately before and one immediately after the operation date of each case). Since in each center the same collateral procedures were used throughout, they are automatically matched. Chi-square tests and odds ratios for matched triplets5 were used to evaluate the statistical significance as well as the strength of association.

#### Results

The incidence of technical failures in patients sterilized by the tubal ring was significantly higher than that in patients sterilized with electrocoagulation (Center A), Rocket clip (Center D), or the modified Pomeroy technique (Center F) (Table I). The tubal ring patients also had a higher incidence of technical failures than electrocoagulation patients in Center B and tantalum clip patients in Center E, but the number of failures in

<sup>†</sup>Obesity = 120% or more than the desirable weight.

<sup>\$</sup>NS = Not significant.

these two centers was too small for meaningful comparison. Only the prototype spring-loaded clip showed an incidence of failure similar to that of the tubal ring (Center C).

The reasons reported by the operators for the technical failure in 38 tubal ring patients were (a) surgical complications in 17 cases, (b) preexisting conditions in 13 cases, and (c) instrument deficiency in eight cases (Table II).

In all but seven failures, sterilization was completed by changing the technique but still using the original approach. In most cases, the alternate technique was the one being used for comparison in that center, apparently because of the operator's experience and the convenience of equipment. The other seven failures were more serious: two laparoscopic procedures were completed by subsequent laparotomy (one failure was due to transected tubes, the other to pelvic adhesions), and in five cases (two via laparoscopy and three via culdoscopy) the procedure was abandoned without resort to other techniques.

The outcome in the 38 tubal ring patients with technical failure was assessed by comparison with the outcome in the remaining 997 tubal ring patients without failure. These two groups had a generally similar distribution by surgical approach. It is not surprising that the failure patients had (a) a much higher rate of surgical complications and surgical difficulties since, in many cases, these were the conditions that led to the change in technique, (b) a longer operation time as a result of the change, and (c) a longer hospitalization after the sterilization procedure, which may have been, in part, a result of the more frequent use of general anesthesia in the failure patients (44.7%) than in the patients without failure (18.4%). What is surprising is the lower early complication rate reported at the 7- to 21-day follow-up visit by the failure patients (9.1%) than by the nonfailure patients (20.0%) (Table III).

Thirty-six tubal ring patients with technical failures were each successfully matched with two controls; operators could not be matched for the other two patients. The following risk factors were delineated in association with the ring failures, and their respective odds ratios were calculated: obesity\* (7.50), prior use of an intrauterine contraceptive device (IUD) (6.00), and history of abdominal operation (3.50) (Table IV).

Besides age, which was matched at the outset, the mean parity and the husbands' mean level of education

\*Obesity was defined as 120% or more of the desirable weight for different heights, with use of the Metropolitan Life Insurance Company's actuarial tables for women.<sup>6</sup>

were similar between cases and controls. Reported incidences of induced abortions were low in both groups. Prevalence of pelvic infection\* was higher in the cases, but the difference was at borderline significance (0.05 ; odds ratio = 2.67). However, the proportion of women who previously used oral contraceptives was significantly lower in cases than in controls <math>(p < 0.05), odds ratio = 0.46).

When the triplets were broken down by the reported reasons for failure of the case member, failures due to complications during the procedure were significantly associated with prior use of an IUD, failures due to preexisting conditions were associated with prior use of an IUD, as well as a history of abdomical operation; and failures due to instrument problems were associated with obesity (Table IV).

#### Comment

Pooling data on tubal ring patients from the six comparative studies gives a technical failure rate of 3.7 per 100 procedures, which is identical to the surgical complication rate. Thus, ignoring the incidence of technical failures when evaluating a sterilization technique is not justified.

Use of the tubal ring for sterilization is associated with a statistically higher technical failure rate than use of electrocoagulation, the Rocket clip, or the modified Pomeroy technique. This finding cannot be attributed to differences in characteristics of the patients, since random allocation eliminates this potential bias. However, since each of these results came from a single center, similar comparative studies in other centers are needed to ensure that these findings were not a result of a center effect.†

The actual reason for the technical failures may not be so clear-cut as reported, since most failures probably were caused by an interplay among the host factors, the operator's skill, and the instrument used. Tubal transections, for example, may have been due to a combination of adhesions, lack of operator experience, and difficulty with the instrument. However, analysis of risk factors by a breakdown of the technical failures according to reported reasons yielded results with biologic plausibility, and it appears that the operators' report of the primary reason for technical failure carries considerable validity.

\*Pelvic infection was defined as any infection of the uterus, adnexa, or other pelvic organs. This definition is admittedly vague, and there may be some variations in diagnostic criteria used among the study centers.

†For instance, in Center A, there was concern that training in the tubal ring technique was not adequate.

Technical failures can also be due to the surgical approach.\* However, the majority of the technical failures in the ring patients can be attributed to the ring technology itself. Close to half of these failures were due to tubal tears, a common complication due to the necessary mobilization of the tube for application of the ring.7

In spite of the difficulties encountered during the operation, fewer tubal ring patients with technical failures than nonfailure patients reported early complications. There are at least three possible explanations for this interesting finding: (a) when surgical conditions indicate the need for a change in operative technique, it is to the patient's benefit to change to another procedure; (b) patients who had a change in operative technique received more attention and perhaps better care; or (c) the techniques that were used to complete the procedure are associated with a lower early complication rate.

Tubal ring patients with technical failures had a lower 6-month follow-up rate (47.4%) than those with no failures (80.6%). No poststerilization pregnancies. were reported by the former, whereas five pregnancies were reported by the latter group.

One risk factor, obesity, was the reason for four of the eight failures due to instrument problems—the trocar was not long enough to reach the peritoneal

The second risk factor, prior use of an IUD, was associated with technical failures that were reportedly due to either surgical complications or patients' preexisting conditions. Previous studies have suggested that use of an IUD is one of the etiologic factors in pelvic inflammatory disease. 5-13 In this study, 38.7% of the users of an IUD and 25.9% of the nonusers had pelvic infection, a statistically nonsignificant difference. It is possible that in some cases the prior use of an IUD could have caused tubal changes in the absence of clinically overt pelvic infection and may have contributed to these technical failures. Discretion should be employed in regard to tubal ring sterilization in a patient who has used an IUD. Prior use of oral contraceptives was significantly less frequent among cases than among controls, but the strength of its negative association with ring failures is much weaker than that of the positive association of IUD use. Whether the use of oral contraceptives, as some studies have suggested, 14, 15 may exert some protective effect against pelvic infection,

\*For instance, at Center E, all three failures, in which the sterilization procedures were not completed, were sterilizations attempted via culdoscopy, thus illustrating the reduced maneuverability in that approach.

and, hence, technical failures in tubal ring sterilization, needs to be clarified.

The third risk factor, previous abdominal operations, is associated with technical failures claimed to be due to conditions preexisting in the patients. Eleven patients included in the case-control analysis had previously undergone abdominal operations (nine had had an appendectomy, one had had a cesarean section and an appendectomy, and one had had an abdominal. bladder operation); seven were failure cases and only four were controls (the expected number of controls is 14, under the null hypothesis). The outcome of the seven failure cases was more serious: in only three patients was the sterilization completed by changing the technique, two required laparotomy for completion of the procedure, and sterilization could not be completed in two. This finding suggests that caution must be used when patients with previous abdominal operations undergo tubal ring sterilization procedures, especially those done via laparoscopy or culdoscopy.

Results from any case-control study should be reviewed carefully for possible biases. Our data were from prospectively conducted clinical trials, and information on all possible risk factors was obtained before sterilization. Technical failure, the dependent variable, is a clear-cut surgical event, which could categorize the cases and the controls with little ambiguity. Careful matching has further eliminated most of the important confounding variables, including operators and their experience. 16, 17 The weakness of this study is the lack of a wider range of detailed information to confirm the possible causal role of the risk factors identified. The small number of triplets, as well as the heterogeneity of the technical failures with regard to their reported reasons, prevented us from attempting a multivariate analysis. However, the fact that only six of the 36 failure cases simultaneously possessed two of the three identified risk factors, and that the odds ratio increased to 12.0 for these patients suggests that the effects of these risk factors on ring failures are generally independent and probably additive.

Confirmation of whether the findings from this case-control analysis of tubal ring sterilization are applicable to other tubal occlusion techniques awaits the results from similar studies on other techniques. However, it would not be surprising to find similar risk factors delineated, possibly with different strengths of associations because of the particular characteristics of each of these techniques.

We would like to thank Dr. Lawrence L. Kupper for reviewing the draft of this paper.

#### REFERENCES

- 1. Wortman, J.: Tubal sterilization—Review of methods, Popul. Rep. (C) No. 7, 1976.
- 2. Hulka, J. F.: Relative risks and benefits of electric and nonelectric sterilization techniques, J. Reprod. Med. 21:111, 1978.
- 3. Kessel, E., Pachauri, S., and McCann, M. F.: A comparison of laparoscopic tubal occlusion by cautery, spring-leaded clip and tubal ring, *in Sciarra*, J. J., Droegemueller, W., and Speidel, J. J., editors: Advances in Female Sterilization Techniques, Hagerstown, 1976, Harper and Row, p. 69.
- 4. Cni, I-c., Laufe, L. E., Gardner, S. D., and Tolbert, M. A.: An epidemiologic study of risk factors associated with pregnancy following female sterilization, Am. J. Obstet. Gynecol. 136:768, 1980.
- 5. Fleiss, J. L.: Statistical methods for rates and proportions, New York, 1973, John Wiley & Sons, Inc, p. 80.
- 6. Metropolitan Life Insurance Company: New weight standards for men and women, Statistical Bulletin 40:1, November-December, 1959.
- Yoon, I. B., and King, T. M.: The laparoscopic Falopering procedure, in. Sciarra, J. J., Droegemueller, W., and Speidel, J. J., editors: Advances in Female Sterilization Technology, Hagerstown, 1974, Harper & Row, Publishers, p. 4.
- Guillebaud, J.: Pelvic inflammatory disease and IUCDs, Br. I. Fam. Plann. 4:25, 1978.
- 9. Westrom, L., Bengtsson, L. P., and Mardh, P.: The risk of pelvic inflammatory disease in women using intrauterine contraceptive devices as compared to nonusers, Lancet 2:221. 1979.

- Targum, S. D., and Wright, N. H.: Association of the intrauterine device and pelvic inflammatory disease: A retrospective pilot study, Am. J. Epidemiol. 100:262, 1974
- Guillebaud, J.: The safety of intrauterine devices, Stud. Fam. Plann. 10:174, 1979.
- 12. Phaosavasdi, S., Vivanichakul, B., Rienprayura, D., et al.: Pelvic inflammatory disease in contraceptive acceptors disclosed at transvaginal tubal sterilization, in Hefnawi, F., and Segal, S. W., editors: Analysis of Intrauterine Contraception, New York, 1974, North-Holland/American Elsevier Publishing Co., p. 397.
- Wright, N. H.: Unsuspected pelvic infection discovered at tubal ligation: Relationship to use of intrauterine contraception, in Hefnawi, F., and Segal, S. W., editors: Analysis of Intrauterine Contraception, New York, 1974, North-Holland/American Elsevier Publishing Co., p. 401.
- Wright, N. H.: Natural history of contraceptive practice among postpartum loop acceptors, Obstet. Gynecol. 33:3361, 1969.
- 15. Eschenbach, D. A., Harnisch, J. P., and Holmes, K. K.: Pathogenesis of acute pelvic inflammatory disease: Role of contraception and other risk factors, Am. J. Obstet. Gynecol. 128:838, 1977.
- Laufe, L. E., and McCann, M. F.: Training: An integral adjunct to introduction of newer methods of fertility control, Int. J. Gynaecol. Obstet. 15:302, 1978.
- Wortman, J., and Piotrow, P. T.: Laparoscopic sterilization. II. What are the problems? Popul. Rep. (C) No. 2, 1973.

## Trophoblastic disease monitoring: Evaluation of pregnancy-specific $\beta_1$ -glycoprotein

TIMOTHY J. O'BRIEN
EVA ENGVALL
J. B. SCHLAERTH
C. PAUL MORROW
Los Angeles and La Jolla, California

Pregnancy-specific β<sub>1</sub>-glycoprotein (SP<sub>1</sub>) was evaluated as a potential marker protein for monitoring trophoblastic disease. Four patients with post-molar pragnancy accompanied by spontaneous titer remission and three patients with nonmetastatic trophoblastic disease were found to have regression curves for both human chorionic gonadotropin (hCG) and SP<sub>1</sub> which closely followed each other. Of three patients with metastatic choriocarpinoma, two were shown to have discordant hCG and SP<sub>1</sub> patterns. SP<sub>1</sub> in both cases was plateauing or rising while hCG continued to fall. Two other patients are described, one with a spontaneous remission, and one who previously had had choriocarcinoma and was found to have low levels of hCG with higher levels of SP<sub>1</sub>. (AM. J. OBSTET. GYNECOL. 138:313, 1980.)

RADIOIMMUNOASSAY (RIA) of human chorionic gonadotropin (hCG) is routinely and successfully used to monitor therapy in patients with choriocarcinoma. For this purpose, hCG can be regarded as the model tumor marker. However, the shortcomings associated with the use of hCG-RIA1 are based on the chemical similarities of hCG to other hormones. Even antisera raised against the isolated beta subunit of hCG cross react to some extent with luteinizing hormone (LH) because of the homologoes amino acid sequence in the beta subunits of these hormones. Therefore, high levels of LH may interfere with the quantitation of low levels of hCG. Although more specific antisera to hCG have been produced, in recognition of the unique carboxy terminal amino acid sequence of  $hCG_{\beta}$ , the resulting assays have proved to be less sensitive.

> From the Department of Obstetrics and Gynecology, University of Southern California School of Medicine, and La Jolla Cancer Research Foundation.

Supported by Wright Foundation Grant No. 55 and National Institutes of Health Grant No. 2R18CA 20749-04 to Dr. Morrow and Dr. O'Brien; and by National Cancer Institute Grant No. CA 27464 to Dr. Engvall.

Received for publication April 3, 1980. Accepted June 18, 1980.

Reprint requests: Dr. Timothy J. O'Brien, Department of Obstetrics and Gynecology, Women's Hospital, L903, 1240 North Mission Rd., Los Angeles, California 90033.

Because of some of the problems inherent in hCG-RIA, other products of the normal and malignant trophoblast should be evaluated as potential tumor markers. Pregnancy-specific  $\beta_1$ -glycoprotein  $(SP_1)^{3,-4}$  is a strong candidaté for supplementing hCG in this respect. Indeed, several reports describe the use of assays for SP<sub>1</sub> as an adjunct to assays for hCG in monitoring. trophoblastic tumor activity,4-7 as well as in monitoring normal or abnormal pregnancy.8-10 Overall, these studies show that SP<sub>1</sub> provides a sensitive measure of pregnancy and trophoblastic tumors, but in most instances, assays for SP<sub>1</sub> were found to be less sensitive than assays for hCG in detecting these conditions. On the other hand, in some individuals, SP<sub>1</sub> may be present in the absence of hCG and may, potentially, be more discriminatory than hCG.

We have further explored the potential of SP<sub>1</sub> in monitoring trophoblastic disease by sequentially measuring levels of SP<sub>1</sub> in 12 patients under surveillance at the Western Trophoblastic Disease Center, and comparing the SP<sub>1</sub> levels in these patients with the hCG levels. In agreement with previous studies, we found a close correlation between SP<sub>1</sub> and hCG levels in most of the patients during the course of treatment. In general, SP<sub>1</sub> seems to be less sensitive than hCG as an indicator of disease. However, in some cases, SP<sub>1</sub> and hCG show discordant behavior. Although at present these results cannot be used to the benefit of the patient, further

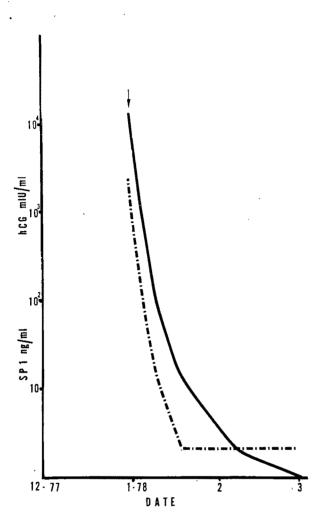


Fig. 1. C. G., a 15-year-old primigravid girl, underwent suction curettage for hydatidiform mole in December, 1977 (uterine size = 14 weeks, gestational age = 27 weeks). Both the hCG and SP<sub>1</sub> titers dropped promptly after evacuation to nondetectable levels. hCG reached the maximum sensitivity level after approximately 2 months, and the SP<sub>1</sub> titer disappeared within 5 weeks. The patient became pregnant in November, 1978, and underwent a spontaneous abortion. In May, 1979, she again became pregnant and was delivered of a term infant. The patient is proceeding well at the present time. Solid line = hCG; dashed line = SP<sub>1</sub>; arrow = suction curettage.

studies may show that low or negative levels of SP<sub>1</sub> are more conclusive than low levels of hCG.

#### Material and methods

Collection and storage of samples. Blood was collected without additives and stored at  $+4^{\circ}$  C. Serum was removed within one day and stored at  $-20^{\circ}$  C until analyzed.

Radioimmunoassays of hCG and SP<sub>1</sub>. Purified  $\beta$  subunit of hCG (Lot CR119-2) was a gift from Drs. Robert Canfield and Griff Ross. Antiserum to the  $\beta$ 

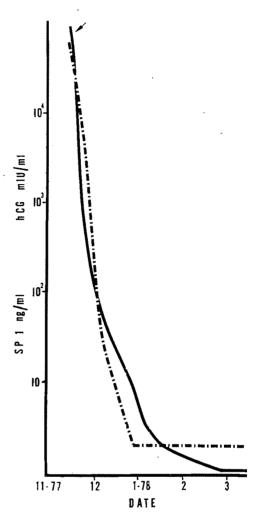


Fig. 2. T. C., an 18-year-old primigravid girl, underwent evacuation of a hydatidiform mole in November, 1977 (uterine size = 18 weeks, gestational age = 25 weeks). The hCG and  $SP_1$  titers fell quickly, reaching baseline within just over 2 months for hCG and within 6 weeks for  $SP_1$ . The patient has been in stable remission since that time. Solid line = hCG; dashed line =  $SP_1$ ; arrow = suction curettage.

subunit was raised in rabbits, and a radioimmunoassay was developed with the use of hCG purchased from Boehringer Mannheim Biochemicals. Iodination of the hCG molecule was carried out monthly by the Chloramine-T method. Incubation of the primary antibody with the iodinated antigen and cold standard or sample was done in 250  $\mu$ l of buffer (0.05M Tris, 0.025M ethylenediaminetetra-acetic acid, 0.5% bovine serum albumin) overnight at 4° C. Second antibody (goat antirabbit IgG) was then added (100  $\mu$ l, 1 to 10 dilution) along with carrier normal rabbit serum (50  $\mu$ l, 1 to 8 dilution). After incubation for 2 hours at 4° C, 1 ml of cold buffer was added and the tubes were centrifuged at 2,000 × g for 30 minutes. The supernatant was aspirated and the pellets were counted in a Nuclear-

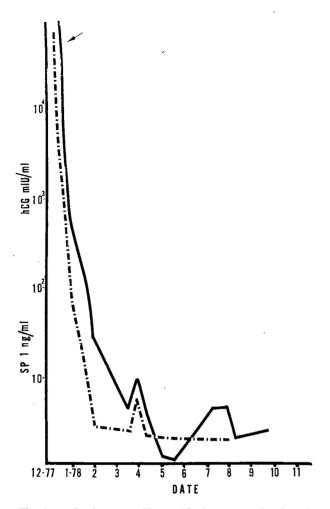


Fig. 3. B. C., 24 years old, gravida 2, para 1, abortions 0, underwent evacuation of a molar pregnancy by suction curettage in December, 1977 (uterine size = 18 weeks, gestational age = 13 weeks). Before evacuation the titer for serum hCG was 592,000 mIU/ml, and for SP1 it was 55,000 ng/ml. Chest x-ray findings were normal. Large theca-lutein cysts were present in both ovaries. Oral contraceptives were prescribed. Both the hCG and SP<sub>1</sub> levels fell through mid-March, when she had a transient elevation in both hCG and SP<sub>1</sub>. SP<sub>1</sub> levels reached baseline in May, and hCG levels, in June. Persistently low levels of hCG were found from July through October, and during this time the SP1 was not detectable. The patient was referred to the prenatal clinic in October, 1979, with a normal pregnancy at 3 months' gestation. Solid line = hCG; dashed line =  $SP_1$ ; arrow = suction curettage.

Chicago Gamma Counter. The sensitivity of the assay was less than 1 mIU (0.4 ng) per milliliter and had an LH cross reactivity of 7% at 50% binding. Boehringer hCG (Lot 1368101) was standardized against National Institutes of Health hCG standard and was used for the whole study.

SP<sub>1</sub> was purified from placental extracts, 11 and antisera were raised in rabbits. Double antibody radioimmunoassay was performed as described by Engvall and

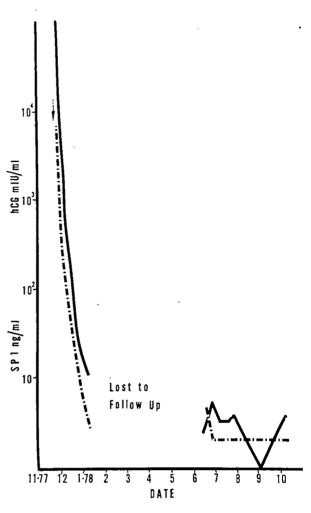


Fig. 4. M. A., 22 years old, gravida 2, para 1, abortions 0, underwent suction curettage for hydatidiform mole in November, 1977 (uterine size = 18 weeks, gestational age = 25 weeks). After evacuation the hCG and SP1 titers continued to fall through January 9, 1978, at which time she was lost to follow-up. She subsequently presented for medical care in June, 1978, and continued to have low titers of hCG ranging from 1.6 mIU/ml to 5.2 mIU/ml. Initially, she also showed a detectable SP, titer, but this returned to baseline by the end of June, 1978. She continued to show low titers of hCG through February, 1979, during which period she was maintained on oral contraceptives. Simultaneous LH levels during this period were all <1.5 mIU/ml. The patient was again lost to folow-up in March, 1979. Solid line = hCG; dashed line =  $SP_1$ ; arrow = suction curettage.

Yonemoto,12 except that samples of serum were tested at a 1 to 10 dilution, and total volume was 1 ml. The lower limit of detection was 2 ng of SP<sub>1</sub> per milliliter of serum. Interassay variation was less than 20% in the range of 2 to 50 ng/ml.

#### Results

For purposes of analysis, the study patients were divided into four separate groups: (1) post-molar preg-

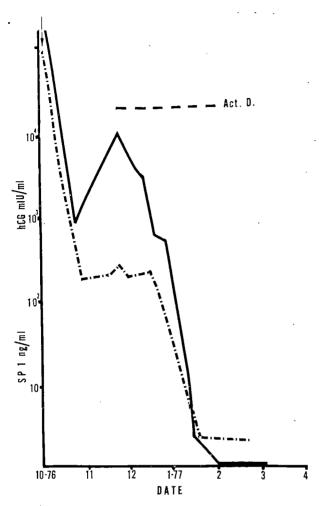


Fig. 5. V. M., 16 years old, gravida 1, para 0, abortions 0, underwent suction curettage for a hydatidiform mole in October, 1976 (gestational age = 30 weeks). Toxemia accompanied the pregnancy. Oral contraceptives were prescribed. The titers before evacuation were 283,000 mIU/ml for hCG and 48,000 ng/ml for SP<sub>1</sub>; these fell to 670 for hCG and 150 for SP<sub>1</sub> 2 weeks after evacuation. The hCG titer then rose steadily to 6,900 despite a second curettage. The SP<sub>1</sub> titer leveled off at 150 to 200 ng/ml. Five-day courses of actinomycin D chemotherapy were given on six occasions from November 23, 1976 to January 31, 1977, during which time the hCG and SP<sub>1</sub> values dropped to baseline. Diagnosis: postmolar, nonmetastatic trophoblastic disease. Solid line = hCG; dashed line = SP<sub>1</sub>; arrow = suction curettage; *Act. D* = actinomycin D treatment.

nancy with spontaneous titer remission; (2) nonmetastatic trophoblastic disease; (3) metastatic choriocarcinoma; and (4) unusual cases.

In Group 1 (Figs. 1 through 4), two types of patient were seen. Patients C. G. and T. C. (Figs. 1 and 2) had relatively low initial levels of hCG and SP<sub>1</sub> and showed a prompt decrease in both markers after molar evacuation. Levels of hCG before evacuation were higher than those of SP<sub>1</sub> (13,000 mIU/ml hCG compared to

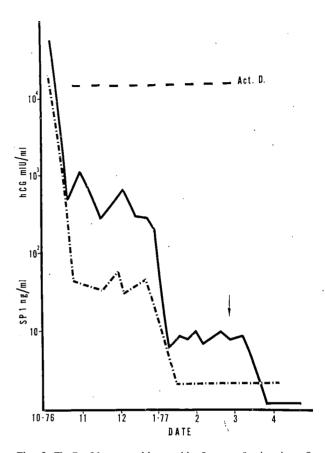


Fig. 6. T. C., 31 years old, gravida 6, para 3, abortions 2, underwent evacuation of a hydatidiform mole by suction curettage in October, 1976. After an initial drop in both the hGG and  $SP_1$  titers through November 10, the hCG titer began to rise and the  $SP_1$  titer plateaued. At this time, single-agent chemotherapy (Act. D) was begun and continued until March, 1977. By that time the hCG titers had reached a low but detectable level (5 to 10 mIU/ml) and the  $SP_1$  levels had reached baseline. On March 2, 1977, the patient underwent a hysterectomy which revealed no evidence of trophoblastic disease. The hCG titer became nondetectable thereafter. Solid line = hCG; dashed line =  $SP_1$ ; arrow = vaginal hysterectomy; Act. D = actinomycin D treatment.

2,200 ng/ml  $SP_1$  for Patient C. G.; 74,000 mIU/ml hCG compared to 47,000 ng/ml  $SP_1$  for Patient T. C.) and remained higher during the precipitate drop in both markers within 6 weeks of evacuation. In these patients,  $SP_1$  became undetectable before hCG.

The second two patients in Group 1, B. C. and M. A. (Figs. 3 and 4), started out with somewhat higher levels of hCG and SP<sub>1</sub> before evacuation, but both levels decreased rapidly after evacuation. However, both patients showed fluctuating low levels of hCG, mostly in the absence of SP<sub>1</sub>. Fig. 3 shows a transitory rise in hCG in April, 1978, accompanied by a similar rise in SP<sub>1</sub>. However, a later elevation of the hCG level to 4 or 5 mIU/ml in July and August, 1978 was not accom-

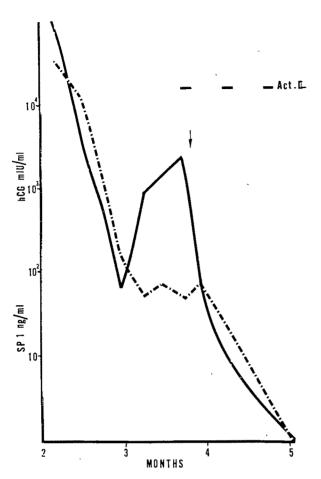


Fig. 7. J. P., 31 years old, gravida 9, para 8, abortions 0 underwent suction curettage for a hydatidiform mole in Feb ruary, 1977 (uterine size = 17 weeks, gestational age = 17 weeks). The pre-evacuation titers of 368,000 mIU/ml for hCC and 35,000 ng/ml for SP1 dropped quickly through February 27. In March, the hCG level plateaued and actinomycin L treatments were begun. A vaginal hysterectomy was performed on March 23. Pathologic examination of the uterus revealed choriocarcinoma. The hCG and SP1 titers returned to baseline by May, 1977. Solid line = hCG; dashec line =  $SP_t$ ; arrow = vaginal hysterectomy; Act. D = actinomycin D treatment.

panied by a similar elevation in the SP, level, a finding which may indicate a discordance between hCG and SP<sub>1</sub> secretion or production. Fig. 4 also shows low fluctuating levels of hCG in the absence of SP<sub>1</sub>.

Three patients with post-molar, nonmetastatic trophoblastic disease (Group 2) were monitored for hCG and SP<sub>1</sub> (Figs. 5 through 7). Characteristic of this group of patients were a plateau and/or a rise in the levels of both SP<sub>1</sub> and hCG. In this sense, SP<sub>1</sub> appeared to correlate very closely with hCG as a marker for trophoblastic disease. An exception is shown in Fig. 6, in that a second plateau of hCG levels between 5 and 10 mIU/mI was not detectable by monitoring SP<sub>1</sub>.

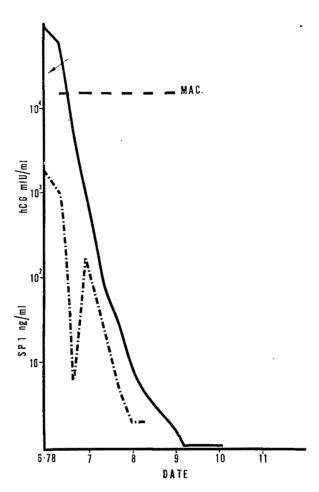
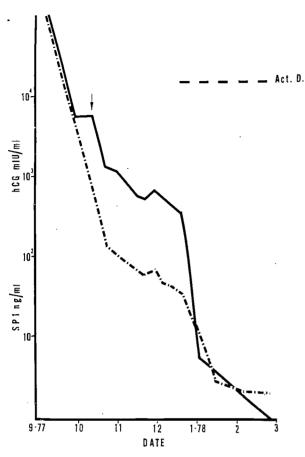


Fig. 8. G. A., 28 years old, gravida 5, para 4, abortions 1, underwent a laparotomy for a tubal ectopic pregnancy in May, 1978. Postoperatively, the patient continued vaginal bleeding and positive pregnancy tests. On May 31, 1978, a chest x-ray film revealed a metastatic nodule; ultrasound of the abdomen revealed a uterus consistent in size with a 16week gestation. Suction curettage was performed but no molar tissue was obtained. Pathologic examination revealed tissue consistent with choriocarcinoma. The patient's previous pregnancy terminated in the birth at term of a female infant on November 17, 1974. A pelvic angiogram revealed a vascular mass in the uterus, as well as liver metastasis. Combination chemotherapy (MAC.) was begun on June 10, 1978, and the patient received six courses. During June and July, the hCG titers continued to decline; however, the SP<sub>1</sub> titer showed a significant increase in late June before returning to baseline by August, 1978. The hCG titer had reached baseline by September 1978, at which time all evidence of metastasis had disappeared. Solid line = hCG; dashed line = SP1; arrow = suction curettage; MAC. = methotrexate actinomycin D cytoxan treatment.

Group 3 patients with metastatic choriocarcinoma are presented in Figs. 8 to 10. As in Group 2, these patients were characterized by a plateau or a less precipitate decrease in levels of SP1 and hCG. In two of these cases, a discordant hCG and SP<sub>1</sub> profile were



**Fig. 9.** M. M., 24 years old, gravida 2, para 1, abortions 0, underwent suction curettage for hydatidiform mole in September, 1977 (uterine size = 24 weeks, gestational age = 13 weeks). After evacuation, the hCG and SP titers dropped through September, 1977, but they plateaued in October, 1977. The patient was started on chemotherapy in December, 1977, and received five courses. A chest x-ray film on January 3, 1978, revealed a metastatic nodule of the lung. hCG and SP<sub>1</sub> titers reached baseline levels in February, 1978. The patient continues to be in stable remission. Solid line = hCG; dashed line = SP<sub>1</sub>; arrow = curettage; *Act. D* = actinomycin D treatment.

noticed. Fig. 8 shows hCG levels that continue to drop at a regular rate during the course of chemotherapy. In contrast, a rise in SP<sub>1</sub> occurred during the early phases of the therapy (June and July, 1978). Similarly, Fig. 10 shows that SP<sub>1</sub> levels plateau or rise slightly while hCG levels continue to drop. In Fig. 9, both markers essentially follow the same profile.

Group 4 represents two patients who were considered unusual enough to be placed in a special category. The first patient (Fig. 11) had been treated for gestational choriocarcinoma in 1972, and had been in remission on oral contraceptives for 6 years. After she discontinued the contraceptives in June, 1979, she missed a menstrual period in July. Because of vaginal bleeding in August, a determination of serum hCG was

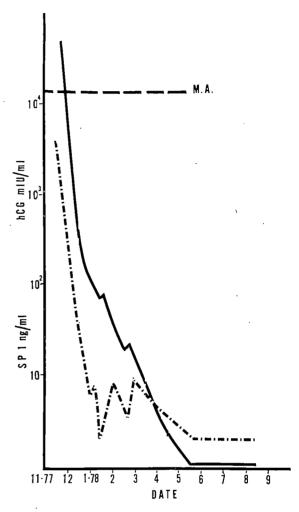


Fig. 10. B. B. was delivered of a molar pregnancy in December, 1976. In early 1977, she was treated for choriocarcinoma with metastasis to the liver and the brain, with radiation therapy to the brain and combination chemotherapy. However, she was lost to follow-up during therapy. After an interval of 9 months, she presented again in November, 1977, with bright red blood in the stools. Chest x-ray examination revealed multiple bilateral metastases. A liver and spleen scan revealed two defects compatible with metastasis to liver. Computerized tomography of the brain again revealed an occipital-parietal lesion on the left side. Angiography of the intestinal tract revealed a bleeding point from a metastasis in the distal small bowel. The patient received 13 courses of actinomycin D and methotrexate in combination between November 1, 1977 and May 15, 1978. At the time that chemotherapy was discontinued, all evidence of metastasis had disappeared and the beta hCG titer was negative. On May 8, the hCG and SP1 titers were nondetectable for the first time. The patient has been in stable remission since that time. Solid line = hCG; dashed line =  $SP_1$ ; M.A. = methotrexate and actinomycin D treatment.

performed and was found to be 122 mIU/ml, but the pelvic examination gave normal findings. It was assumed that she had an early spontaneous abortion. She was again started on oral contraceptives. During the ensuing 4 months, the hCG levels varied between 10

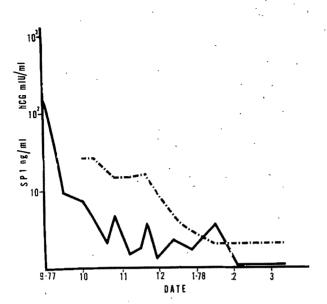


Fig. 11. L. M., 27 years old, was treated with actinomycin Γ, methotrexate, and cyclophosphamide for gestational choriccarcinoma in 1972. In June, 1977, she discontinued taking oral contraceptives in order to conceive. She had no menstruperiod in July. In August, she experienced some vagin. I bleeding. Serum hCG in late August was 122 mIU/ml. From September 15 to November 7, the hCG titer fell from 9.5 to 1.4 mIU/ml. It remained between 1.5 and 3.3 from then untl February 1, 1978. During this time the serum LH was consitently <1.5 mIU/ml. On February 1, 1978, the serum hC3 was <1.0 mIU/ml and remained <1.0 on monthly determsnations through August, 1978. During this latter period the SP<sub>1</sub> titer went from 26 ng/ml on September 29, 1977, 10 baseline (2 ng/ml) in January, 1978. Solid line = hCG; dashed line =  $SP_1$ .

and 1.5 mIU/ml before becoming undetectable in February, 1978. During this entire period, the SP<sub>1</sub> levels exceeded the hCG levels (26 ng/ml SP1 compared to 9.3 mIU/ml hCG on September 30).

The second patient in Group 4 (Fig. 12) was undergoing chemotherapy for the second relapse of metastatic choriocarcinoma. In June, 1976, when the titehad reached 3 mIU/ml, she refused further drug treatment. A vaginal hysterectomy was performed and residual choriocarcinoma was identified During 1977. the hCG levels rose above 100 mIU/ml and SP1 reaches. 70 ng/ml. By the end of the year, the levels of eacL marker decreased; and by November, \_978, the hCG was down to 32 mIU/ml and the SP₁ was undetectable Fourteen months later, even hCG was undetectable During this time, the patient received no therapy.

#### Comment

In this study, the regression profiles of SP1 both in patients with benign hydatidiform mole and in patient: with local and metastatic trophoblastic disease all

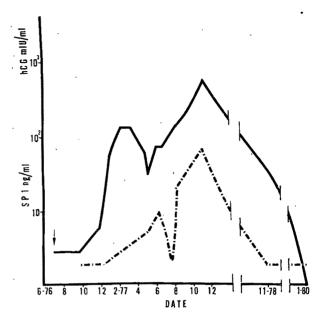


Fig. 12. L. L., 28 years old, had gestational choriocarcinoma metastatic to the lung. She had titer remission (serum hCGβ) on methotrexate in 1973 after a molar pregnancy. In 1974, the titer rose to 103 mIU/ml and she was treated with methotrexate, actinomycin D, and cyclophosphamide until the first normal hCG titer (<5 mIU/ml). Oral contraceptives were prescribed from the time of termination (hysterectomy) of the molar pregnancy. Subsequently the serum hCG titer rose to 138 mIU/ml on March 2, 1976. Chest x-ray examination revealed two discrete lung nodules. On April 13, 1976, chemotherapy was begun with actinomycin D and Velban. After three courses, the titer fell to 3 mIU/ml (June 21, 1976) but she refused further chemotherapy. On June 29, a hysterectomy was performed and an area suspicious for residual choriocarcinoma was identified. The serum hCG titer ranged from 3 mIU/ml (June 29, August 2, and September 27, 1976) to 15 mIU/ml from June 29, 1976 through January 11, 1977, without further treatment. She took no oral contraceptives after the hysterectomy. On May 4, 1977, the serum hCG titer was 42 and it rose to 550 mIU/ml on October 28, 1977. It then fell spontaneously to 251 on December 19, 1977, and <1 on January 19, 1980. Her SP<sub>1</sub> titer remained at baseline between October and December, 1976. An increase in SP1 titer was noticed in early May, 1977, and rose to 68 ng/ml on October 28, 1977. In concert with hCG, it fell to 20 ng/ml on December 19, 1977, and reached baseline on November 8, 1978. Solid line = hCG; dashed line =  $SP_1$ ; arrow = vaginal hysterectomy.

closely resembled the hCG profiles, which is in general agreement with the findings of previous investigations.5-7 These results point favorably to the usefulness of SP<sub>1</sub> as an additional marker of trophoblastic disease and allow for a future unique value of this placental protein in the follow-up monitoring of choriocarcinoma. Possible deficiencies in the use of SP<sub>1</sub> as a trophoblastic tumor marker appear to lie directly in the present sensitivity limit of SP<sub>1</sub> assays. In several cases in our study (Figs. 3, 4, and 6), it was observed that lowlevels of hCG (5 to 10 mIU/ml) were not accompanied by detectable SP<sub>1</sub>. Although there might be several explanations for this disparity, such as the discordant production of SP<sub>1</sub> and hCG during cytotrophoblastic differentiation, the most obvious one is the lack of sensitivity of the assay. However, even more pertinent to the final evaluation of these two trophoblastic tumor markers will be the establishment of accurate background circulating levels of both hCG and SP<sub>1</sub>. Recently, normal hCG values have been reported13 to range from 0 to 361 pg/ml. The upper normal limit of these values, 360 pg/ml (one of 16 subjects) is close to threshold sensitivity (300 to 400 pg/ml) of the standard radioimmunoassay for hCG. Normal circulating levels of SP<sub>1</sub> are rarely detected by means of the present SP<sub>1</sub>-RIA. Only one of 11 individuals with no known trophoblastic disease had more than 2 ng SP<sub>1</sub> per milliliter of serum.11 However, further studies are needed.

Another aspect of the SP<sub>1</sub>-hCG analysis profile can be evaluated by attempting to relate the quantity of glycoprotein secreted to the number and/or type of trophoblastic cells present. The hCG assay presently detects between 10<sup>4</sup> and 10<sup>5</sup> cells at its sensitivity threshold. This number of cells probably represents synctiotrophoblasts which actively synthesize and secrete hCG but which are incapable of cell division, and perhaps, therefore, are of low metastatic potential. If,

on the other hand, SP1 was produced by both the syncytial trophoblast 15 and/or the cytotrophoblast or some invasive predifferentiated form of the syncytial trophoblast, then SP<sub>1</sub> would have unique value as a monitor of metastatic status. Two preliminary kinds of evidence support this suggestion. As reported by Seppala and associates, 16 patients with intrauterine devices who might have transitory pregnancies were shown to have detectable SP<sub>1</sub> levels in six of 94 cycles, whereas the presence of both hCG and SP<sub>1</sub> was found in only one cycle. These data suggest that after implantation of the blastocyst during the invasive phase of early pregnancy, SP<sub>1</sub> is elaborated in relatively greater quantities than hCG. Furthermore, our own data in the metastatic choriocarcinoma group (Figs. 8 and 10) indicate that metastasis or invasion of new tissue sites may well be accompanied by increased levels of SP<sub>1</sub>. In addition, if in the case of L. M. (Fig. 11), the increased SP1 levels were, in fact, due to an early pregnancy which failed to progress, our data would further confirm the elaboration of SP<sub>1</sub> by cells of a presyncytial nature.

In the final analysis, the present study indicates that  $SP_1$  is a potentially useful addition to trophoblastic disease monitoring. The lack of cross reaction with other proteins and discordant expression, compared to hCG, are unique aspects of this marker which make further study of it seem to be worth while.

#### REFERENCES

- Vaitukaitis, J. L., Braunstein, G. D., and Ross, G. T.: A radioimmunoassay which specifically measures human chorionic gonadotropin in the presence of human luteinizing hormone, Am. J. Obstet. Gynecol. 113:751, 1972.
- Vaitukaitis, J. L., and Ross, G. T.: In Saxena, B. B., Beling, C. G., and Gandy, H. M., editors: Gonadotropins, New York, 1972, Wiley-Interscience, p. 435.
- Bohn, H.: Pregnancy-specific β-globulin, SP<sub>1</sub>, in Ruoslahti, E., and Engvall, E., editors: Chemistry of Tumor Associated Antigens, Scand. J. Immunol., Suppl. 6, London, 1978, Blackwell Scientific Publications, pp. 119-125.
- 4. Tatarinov, Y. S.: Trophoblast-specific beta-1-glycoprotein as a marker for pregnancy and malignancies, Gynecol. Obstet. Invest. 9:65, 1978.
- Seppala, M., Rutanen, E., Heikinheimo, M., Jalanko, H., and Engvall, E.: Detection of trophoblastic tumor activity by pregnancy-specific beta-1-glycoprotein, Int. J. Cancer 21:265, 1978.
- Searle, F., Bagshawe, K., Leake, B., and Dent, J.: Serum-SP<sub>1</sub>-pregnancy-specific-β-glycoprotein in choriocarcinoma and other neoplastic disease, Lancet 579:18, 1978.
- Rutanen, E., and Seppala, M.: Pregnancy-specific-β-1glycoprotein in trophoblastic disease, J. Clin. Endocrinol. Metab. 50:57, 1980.
- Gordon, Y. B., Grudzinskas, J. G., Jeffrey, D., Chard, T., and Letchworth, A. T.: Concentrations of pregnancyspecific β<sub>1</sub>-glycoprotein in maternal blood in normal pregnancy and in intrauterine growth retardation, Lancet 1:331, 1977.

- 9. Heikinheimo, M., Unnerus, H. A., Ranta, T., Jalanko, H., and Seppala, M.: Pregnancy-specific beta-1-glycoprotein levels in cholestasis of pregnancy, Obstet. Gynecol. 52:276, 1978.
- Mandelin, M., Rutanen, W., Heikinheimo, M., Jalanko, H., and Seppala, M.: Pregnancy-specific beta-1-glycoprotein and chorionic gonadotropin levels after first-trimester abortions, Obstet. Gynecol. 52:314, 1978.
- 11. Engvall, E.: Pregnancy specific  $\beta_1$ -glycoprotein (SP<sub>1</sub>). Purification and partial characterization, Dev. Biol. Med. In press.
- Engvall, E., and Yonemoto, R. H.: Is SP<sub>1</sub> (pregnancy specific β<sub>1</sub>-glycoprotein) elevated in cancer patients? Int. J. Cancer 23:759, 1979.
- Borkowski, A., and Muquardt, C.: Human chorionic gonadotropin in the plasma of normal, non-pregnant subjects, N. Engl. J. Med. 301:298, 1979.
- 14. Morrow, C. P., O'Brien, T. J., and Schlaerth, J.: Is hCG the ideal tumor marker? *in* Ballen, S., editor: Controversies in Obstetrics and Gynecology. In press.
- Horne, C., Towler, C., Pugh-Humphreys, R., Thomson, A., and Bohn, H.: Pregnancy-specific β-1-glycoprotein— A product of the syncytiotrophoblast, Experientia 32: 1197, 1976.
- Seppala, M., Rutanen, E., Jalanko, H., Lehtovirta, P., Stenman, U., and Engvall, E.: Pregnancy-specific β<sub>1</sub>-glycoprotein and chorionic gonadotropin-like immunoreactivity during the latter half of the cycle in women using intrauterine contraception, J. Clin. Endocrinol. Metab. 47:1216, 1978.

## Vaginal intraepithelial neoplasia: Biologic aspects and treatment with topical 5-fluorouracil and the carbon dioxide laser

EDMUND S. PETRILLI, M.D.
DUANE E. TOWNSEND, M.D.\*
C. PAUL MORROW, M.D.
CALVIN Y. NAKAO, M.D.\*\*

Los Angeles, California

A review of 41 evaluable patients was made in order to study vaginal intraepithelial neoplasia (VAIN) and to investigate new methods of treatment. Colposcopic examination of the vagina revealed white epithelium alone in 20 patients and white epithelium associated with vascular punctation in 15. No lesion had a vascular mosaic pattern. Most patients had multifocal disease located in the vaginal apex. Iodine staining was positive in six patients with negative colposcopic examinations. Twenty-four patients had severe dysplasia or carcinoma in situ, and 17 had minimal or moderate dyplasia. Associated genital disease occurred in 17 patients with antecedent cervical or vulvar squamous neoplasia, and six additional patients had coexistent lesions. The chronology of vaginal disease that appeared after treatment of cervical neoplasia suggests a persistent but decreasing likelihood of the development of VAIN with the passage of time. In patients followed without therapy, six had spontaneous remission of disease. Treatment was successful in 12 of 15 patients with topical 5-fluorouracil and in nine of 10 patients with the carbon dioxide laser. The advantages of these methods of treatment for patients with VAIN relative to surgical procedures and radiation therapy are considered. (AM. J. OBSTET. GYNECOL. 138:321, 1980.)

INVASIVE squamous-cell carcinoma of the vagina accounts for 1% to 4% of all gynecologic malignancies.<sup>1</sup> Although vaginal intraepithelial neoplasia (VAIN) in-

From the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Women's Hospital, Los Angeles County–University of Southern California Medical Center.

Supported by National Institutes of Health Grants CA 02050, 20795, and 08099.

Received for publication November 9, 1979.

Revised April 4, 1980.

Accepted May 29, 1980.

Reprint requests: Edmund Stephen Petrilli, M.D., Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Georgetown University School of Medicine, 3800 Reservoir Rd., N. W., Washington, D. C. 20007

\*Present address: Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, California.

\*\*Present address: Department of Obstetrics and Gynecology, Emanuel Hospital, Portland, Oregon.

volves an older patient population, in comparison to preinvasive disease of the cervix, the relationship to invasive carcinoma may be similar in both instances.<sup>2, 3</sup> The incidence of VAIN is unknown, but vaginal and cervical carcinomas in situ have been reported at a rate of 0.2 and 36.4 cases per 100,000 women, respectively.4 VAIN is diagnosed in approximately 1% of patients with a history of squamous cell neoplasia of the cervix.5-9 Irradiation, postmenopausal atrophy, cancer chemotherapy, and immunosuppression may also be predisposing factors in addition to cervical neoplasia.10-13 Since visible lesions are unusual, abnormal Papanicolaou smears most commonly indicate the presence of disease, and additional diagnostic procedures are required to identify abnormal areas for tissue biopsy. A histologic diagnosis of premalignant disease of the vagina may not predict biologic behavior, since some lesions may progress to invasive carcinoma and others remain stable or undergo spontaneous remission. 11, 14, 15

Operation and irradiation constitute traditional treatment for this disease. Although 85% to 90% effective, these methods are also associated with substantial

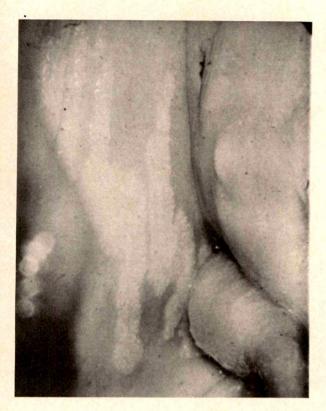


Fig. 1. White epithelium located in right vaginal fornix. Biopsy revealed VAIN I with hyperkeratosis.

**Table I.** Vaginal intraepithelial neoplasia: Distribution of lesions

Vaginal location	Unifocal	Multifocal	Total
Upper third	10	26	36
Mid third	1	0	1
Lower third	0	0	0
Upper, mid, and lower	0	3	3
Upper and mid	0	1	1
Total	- 11	30	41

cost and morbidity.<sup>16–20</sup> This report investigates diagnostic and biologic aspects of vaginal intraepithelial neoplasia and presents the results of current therapeutic approaches with the use of 5-fluorouracil (5-FU) and the carbon dioxide (CO<sub>2</sub>) laser.

#### Material and methods

Sixty patients with preinvasive vaginal neoplasia were seen at the Los Angeles County-University of Southern California (LAC-USC) Medical Center and affiliated private hospitals between 1973 and 1978. The criteria for entry into this retrospective analysis were cytologic smears, colposcopic examination, and tissue confirmation of disease. The hospital records of 41 patients who had an average age of 47 years (range, 19 to 70 years) met these requirements, and 19 did not.



Fig. 2. VAIN III. Colposcopic appearance includes white epithelium with raised surface, sharp borders, and coarse vascular punctation. Biopsy site at 6 o'clock.

Cervical intraepithelial neoplasia (CIN) is a continuum of preinvasive disease.<sup>21</sup> This concept is extended to include vaginal intraepithelial neoplasia (VAIN) and vulvar intraepithelial neoplasia (VIN). The histologic grades of premalignant lesions are: mild dysplasia (I), moderate dysplasia (II), and severe dysplasia or carcinoma in situ (III). Staff pathologists at the LAC-USC Medical Center and affiliated hospitals reviewed all histologic material.

Topical 5-FU\* therapy included a 5 ml test dose of 5% 5-FU cream (one full vaginal applicator) inserted by the patient into the vagina, with examination 4 days later. If no changes occurred in the vaginal membrane, the patient inserted 5 ml of the cream twice daily for 5 days. If the test dose caused ulceration of the lesion, a modified course of 5 ml daily for 5 days was initiated. Because of tissue sensitivity, postmenopausal women were treated for only 4 days. Repeat treatment, if required, began 12 weeks after the initial course. All patients had complete blood and platelet counts, and determinations of blood urea nitrogen, creatinine, bilirubin, alkaline phosphatase, and serum glutamic

<sup>\*</sup>Efudex, Roche Laboratories, Nutley, New Jersey.

Table II. Vaginal intraepithelial neoplasia: Temporal relationship to antecedent squamous cell neoplasia of the lower genital tract

	Treatment for antecedent squamous cell neoplasia				
Interval, in years, to diagnosis of VAIN	Operation	Radiation therapy	Total		
0 - 3	9	0	9		
3 - 10	3	0	3		
10 - 25	2	3	5		
Total	14	3	17		

oxalacetic transaminase in order to screen for systemic toxicity.

CO<sub>2</sub> laser\* therapy was performed at a power setting of 20 watts. Iodine staining of the vagina immediately preceded the continuous application of the laser beam to all areas of abnormal tissue and to a 3 mm margin of surrounding normal tissue. The estimated depth of treatment was 3 to 4 mm below the epithelial surface. Outpatient therapy without analgesia was used in seven patients. Extensive lesions, as well as pain, required treatment under general anesthesia in the other three patients. All patients were examined 8 to 12 weeks after therapy. Successful treatment with the CO<sub>2</sub> laser and 5-FU was defined as the complete disappearance of disease after one or two courses, as determined by normal colposcopy, cytologic examination, and iodine staining. Persistent or recurrent disease after two courses constituted failure.

#### Results

An abnormal cytologic smear led to the discovery of VAIN in 40 of 41 patients. One patient had visible "granulation" tissue which revealed a focus of dysplasia on biopsy. Colposcopic evaluation was positive in 35 patients and negative in six. The lesions in 20 patients manifested white epithelium alone (Fig. 1), and 15 patients had white epithelium associated with vascular punctation (Fig. 2). VAIN I commonly appeared as white epithelium alone, whereas VAIN II and III often had associated punctation. Vascular mosaic patterns were not seen. Iodine staining was recorded in 22 of 41 patients and was positive in every instance, including the six patients who had negative colposcopic examinations. Directed biopsies were graded as follows: VAIN I in 10 patients; VAIN II in 7 patients; VAIN III in 24 patients.

Table I summarizes lesion distribution within the vagina. Disease involved the vaginal apex in 40 patients (98%), and 30 patients (73%) had multifocal lesions. In

Table III. Vaginal intraepithelial neoplasia: Associated squamous cell lesions of the lower genital tract

		, 	
Ante- cedent	Coex- istent	Total	Percent
,			
4*	0	4	10
13	4	17	41
1*	2	3	7
18	6	24	58
	4* 13 1*	## 0 13 4 1* 2	cedent         istent         Total           4*         0         4           13         4         17           1*         2         3

Two of 41 patients had cervical, vaginal, and vulvar disease

only one patient was the upper third of the vagina uninvolved, and she had a focal lesion in the mid-vagina. Three patients had multifocal disease that involved the full length of the vagina.

VAIN followed antecedent cervical or vulvar squamous cell dysplasia or carcinoma in 17 patients (41%); a simultaneous diagnosis of CIN or VIN was made in an additional six patients (15%). The average interval to the development of VAIN in the four patients previously treated for invasive squamous cell carcinoma of the cervix was 17 years (range, 7 to 24 years). Three of these had undergone radiation therapy and developed VAIN III at 14, 23, and 24 years after treatment. All had apical, multifocal lesions in the field of prior irradiation. One of these patients also had undergone a vulvectomy for VIN. The single patient with invasive cervical cancer treated surgically developed VAIN III 7 years later.

Thirteen patients had been previously treated for CIN, including two who also had had prior therapy for VAIN. Of these patients who had antecedent lesions, 14 were treated surgically and one received radiation therapy. The average interval to diagnosis of VAIN in these patients was 4.7 years (range, 0.5 to 21 years). Table II summarizes the intervals between prior treatment and current diagnosis for all 17 patients. The surgically treated group had a decreasing incidence of disease as time progressed, with most VAIN lesions

<sup>\*</sup>Coherent Light System 400 laser and Zeiss operating mi-

<sup>\*</sup>One patient had cervical carcinoma and VIN III.

**Table IV.** 5-FU therapy (N = 15)

Patient	Age (yr)	Courses	Response	Follow-up (mo)
1	49	1	С	2
2	62	1	С	28
3*	55	1	C	7
4	48	1	С	5
5	59	2	С	60
6*	22	1	C	3
7	66	. 1	C	25
8	56	I	С	24
9†	42	2	С	Lost to follow-up
10	55	1	С	6
11	36	1	С	22
12	42	1	С	22
13‡	33	2 -	F	For CO <sub>2</sub> laser
14	58	2	F	CO <sub>2</sub> laser
15	38	2	F	Vaginectomy recommended

C = Complete. F = Failed.

Table V.  $CO_2$  laser therapy (N = 10)

Patient	Age (yr)	Courses	Response	Foilow-up (mo)
16	21	I	С	2
17	31	1	Ċ	11
18	24	1	С	12
19	50	1	С	3
20	69	1	C	6
21	70	2	С	7
22	34	1	$\mathbf{C}$	6
23	47	1	C	4
24	50	2	C	2
14*	58	1	F	Vaginectomy

C = Complete. F = Failed.

presenting within 3 years of therapy for prior genital neoplasia.

Twenty patients had previously undergone hysterectomies, 11 of which were done for CIN. Other indications were, in one patient each, invasive cervical carcinoma, uterine prolapse, and endometrial hyperplasia. In six patients the indications for hysterectomy were unknown. Eleven women had VAIN with uteri in situ and no associated cervical or vulvar neoplasia. Coexistent VAIN and CIN occurred in four of 21 patients at risk; two other patients had VAIN and VIN simultaneously. Histologic grade was the same in four of these six patients. Table III summarizes antecedent and coexistent genital squamous-cell neoplasia. Only two patients had involvement of the cervix, vagina, and vulva, and neither had disease in all three areas simultaneously.

Twenty-four patients were treated with topical 5-FU

or the Co<sub>2</sub> laser, four by outpatient punch biopsy excision, and one with radium. Of 12 patients followed without specific therapy, six had spontaneous remission of disease located in the vaginal apex, in five of whom the lesions were multifocal. The lesions were VAIN I in four patients, and VAIN II and III in one patient each. Three women were premenopausal, and their disease regressed within 6 to 10 months after diagnostic biopsies. Three postmenopausal patients who were treated with topical estrogen cream after diagnostic biopsies had complete regression of disease within 5 to 13 months. All six patients followed without therapy with persistent disease had apical, multifocal lesions, including VAIN III in three patients, VAIN II in two patients, and VAIN I in one patient. In all cases, one or more directed biopsies were obtained from representative areas of abnormality. No lesion was com-Eletely removed by diagnostic biopsy.

Intravaginal treatment with 5-FU was successful in 12 of 15 patients (80%). Apical lesions occurred in 13 patients, and multifocal disease, in 11. The histologic grade was I, II, and III in two, four, and nine patients, respectively, and three had associated hyperkeratosis. Details on the group treated with 5-FU are given in Table IV. Early in the study, three patients experienced severe ulceration of vulvar and vaginal tissues after 7-day courses of 5-FU. This led to the use of the 5 cay course and a test dose of 5-FU, the results of which allowed further modification of dosage when indicated. None of the patients had significant local side effects with this modified regimen. Systemic toxicity did not occur. Patient 9 had previously undergone a partial

<sup>\*</sup>VAIN I. Hyperkeratosis.

<sup>†</sup>Partial vaginectomy 3 years prior to 5-FU therapy. Returned with invasive carcinoma 2 years after treatment with 5-FU.

<sup>‡</sup>VAIN II. Hyperkeratosis.

<sup>\*</sup>Failed 5-FU therapy. Vaginal cuff "tunnel."

vaginectomy for VAIN, and had a complete response of a recurrent lesion to 5-FU therapy. She was lost to follow-up for 2 years and returned with invasive carcinoma deep to the mucosa of the vaginal apex. The patients who were successfully treated have been followed for an average of 18 months.

Nine of 10 patients (90%) had a complete response to CO<sub>2</sub> laser therapy. Nine patients had VAIN III, and one had VAIN I. All lesions were apical in location, and seven were multifocal. Details are presented in Table V. Some patients experienced pain during outpatient therapy. No additional morbidity occurred. Successfully treated patients have been followed for an average of 6 months.

#### Comment

Colposcopy and lesion distribution. The colposcopic appearance of VAIN is white epithelium alone or in association with vascular punctation. The latter is a feature more common to high-grade lesions. Woodruff and associates<sup>22</sup> described vascular punctation in six of nine patients with vaginal carcinoma in situ. In the present report, the most common clinical presentation was apical, multifocal disease, which occurred in two thirds of the cases. Iodine staining is required in the evaluation of patients with VAIN in oder to determine both the presence and location of abnormal tissue, since it alone disclosed disease in six cases. Since the upper third of the vagina was involved in 40 of 41 patients, it is practical to screen the vaginal apex, by colposcopy and iodine staining, of all women who have positive Papanicolaou smears.

Associated genital disease. Field carcinogenesis involving all tissues of the lower genital tract has been postulated to explain the multicentric character and common association of cervical, vaginal, and vulvar squamous cell neoplasia.23-28 A viral etiology has been investigated in this regard, but a causal relationship has yet to be established.29 Interval analysis shows that the largest cluster of VAIN was diagnosed within 3 years after surgical treatment of cervical neoplasia. This suggests that disease may have been present, at least in some patients, at the time of initial therapy. The progressive decrease in cases as the interval increases suggests a persistent but diminished risk of development of VAIN with the passage of time. In this study, the 58% incidence of associated neoplastic disease of the lower genital tract represents a minimum figure because six patients had had hysterectomy for unknown reasons, and it is possible that some had CIN or might have developed it later. Coexistent vulvar disease occurred in 5% and cervical disease in 19% of patients at risk. Two patients had involvement of the cervix, vagi-

na, and vulva, but in neither case were all three areas recognized simultaneously. The combination of vaginal and vulvar lesions without CIN is rare, with only two cases reported in the literature. 30 One additional case occurred in this study. Since VAIN is frequently associated with antecedent or coexistent CIN or VIN, all patients with CIN require careful evaluation of the vagina and vulva.

Relationship to prior radiation therapy. The long latent period of 17 years in three patients who developed VAIN after radiation therapy suggests a different etiologic relationship than VAIN after surgically treated CIN. Intermediate or low-dose irradiation may enhance the risk of subsequent neoplasia because of sublethal injury to adjacent tissues. 10, 31 Another interpretation could be that radiation therapy merely delayed the expression of VAIN. Pride and Buchler<sup>32</sup> studied patients irradiated for cervical carcinoma who developed carcinoma in situ of the vagina more than 10 years later. The average interval to the diagnosis of VAIN was 18.3 years, a finding similar to that in the present report. They concluded that radiation therapy caused a low, but significant, risk for the development of vaginal neoplasia. Palmer and Spratt<sup>31</sup> observed an average interval of 13.8 years between primary radiation therapy for cervical carcinoma and the later occurrence of carcinoma in various adjacent tissues. Data published by Rutledge<sup>14</sup> on vaginal carcinoma in situ that occurred after cervical carcinoma revealed an average interval of 8.4 years in patients treated by irradiation, and 2.8 years in patients treated by hysterectomy. Because previously irradiated patients are at risk for the delayed development of VAIN, indefinite, long-term follow-up is recommended.

Biologic behavior. The spontaneous remission of VAIN, which has been described, 11. 15 occurred in six patients in this study. It is unlikely that inflammation at biopsy sites, as described by Koss and associates,33 was responsible for the resolution of these lesions, because five of the six patients had multifocal disease. Four had VAIN I, which suggests that early-grade lesions may be the most likely to undergo this change. Three patients who were postmenopausal were treated with topical estrogen cream after diagnostic biopsies, since the beneficial effect of estrogen on postmenopausal VAIN has been recognized.<sup>5, 10, 19</sup> Fu and associates<sup>34</sup> correlated nuclear DNA content in CIN lesions with clinical outcome, a method which may predict the biologic behavior of individual VAIN lesions.

Untreated VAIN III can progress to invasive carcinoma.2, 11, 14 One patient in the present study developed invasive disease while lost to follow-up for 2 years. The malignancy was deep to the vaginal surface

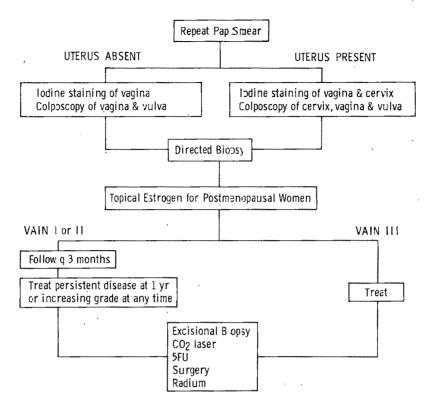


Fig. 3. Evaluation p.ar. for VAIN.

epithelium and may have arisen from dysplastic tissue buried at the time of a previous partial vaginectomy for VAIN. Gallup and Morley<sup>16</sup> suggested such a pathogenesis in regard to a similar case. It is probable that invasive squamous cell carcinoma of the vagina originates from preinvasive intraepithelial lesions. Spontaneous remission of disease appears to be more common with early VAIN than with advanced grades, which may be more likely to progress to invasive carcinoma.

Topical 5-FU. Topical 5-FU was initially used in the treatment of squamous cell neoplasia of the skin.35 Woodruff and associates<sup>22</sup> successfully treated vaginal carcinoma in situ with topical 5-FU in eight of nine patients. The single failure involved a lesion with hyperkeratosis. The present report includes three patients with hyperkeratosis, two of whom had VAIN I, and both responded to 5-FU. In one patient who had VAIN II, treatment failed. Hyperkeratosis may be significant only with higher grade lesions. Three patients had marked ulceration of the vulva and vagina after treatment with 5-FU, thus demonstrating that normal tissues are also sensitive to this agent. The use of a test dose prevented further morbidity. Ballon and associates<sup>36</sup> treated 12 patients with topical 5-FU, and two patients had disease after two courses of therapy. This response rate of 83% is similar to that in the present study, if the same definition is used. Immunotherapy with dinitrochlorobenzene has been used for VAIN<sup>15</sup> but may be less reliable than topical 5-FU.<sup>37–39</sup> 5-FU may be most appropriate for multifocal or extensive VAIN or after failure with the CO<sub>2</sub> laser.

CO laser therapy. Using the CO2 laser, Carter and associates<sup>40</sup> successfully treated 42 of 45 women with CIN, and Staff and associates41 eradicated VAIN in five of six patients. These results are similar to the 90% response rate of the patients in this study. The advantages of the laser over hot cautery and cryotherapy include precise control of tissue destruction, minimum injury to adjacent cells, and decreased inflammation in surrounding tissues, all of which promote optimal healing. Since some patients experienced pain during outpatient therapy, treatment with the patient under general anesthesia may be preferred. The CO<sub>2</sub> laser may best be used for focal VAIN or when 5-FU therapy has failed. The expense of the CO<sub>2</sub> laser unit limits its availability to referral centers where it is most cost effective.

Surgical procedures and radiation therapy. Four patients with focal VAIN were successfully treated by cutpatient excisional biopsy. When possible, this is the preferable method of treatment because it is simple, inexpensive, and lacks morbidity. Partial and total vaginectomy procedures, although effective, require

vaginal plastic reconstruction in order to preserve sexual function, and morbidity may be considerable. <sup>10, 12</sup> A problem peculiar to the treatment of VAIN in the posthysterectomy patient is the "tunnel" often found at either angle of the vaginal cuff which impairs evaluation and treatment, as in Patient 14. Patient 9 developed invasive carcinoma deep to the mucosa of the vaginal apex, which may have resulted from dysplastic epithelium buried at the time of earlier vaginectomy. These cases suggest that patients with distorted vaginal anatomy should have primary surgical therapy in order to assure adequate evaluation of the tissue.

The use of radium as a means of treatment for VAIN may induce ovarian failure in younger patients. Vaginal stenosis may occur, particularly when treatment involves more than the upper third of the vagina. Complications with radiation necrosis, ulceration, and the formation of fistula often require subsequent operative intervention. Although they are as effective as surgical procedures and irradiation, topical 5-FU and the CO<sub>2</sub> laser provide the advantages of cost effectiveness, minimal morbidity, and greater simplicity of use.

Treatment planning. An evaluation plan for patients with VAIN is presented in Fig. 3. Repeat Papanicolaou smears should precede colposcopy, iodine staining, and multiple directed biopsies. Careful assessment for associated genital neoplasia is required. The routine use of topical estrogen for postmenopausal women is recommended. Grade I or II lesions may be observed in reliable patients and treatment instituted if repeat Papanicolaou smears show increasing grade or if disease persists after 12 months. VAIN III requires treatment when diagnosed. Small, focal lesions can be treated most effectively by outpatient excisional biopsy. If this fails, CO<sub>2</sub> laser therapy should be employed. Large or multifocal lesions should be treated initially with 5-FU. Failure with either 5-FU or the CO2 laser should be followed by the alternate method. Surgical intervention should be used only when these simpler methods fail, or if distorted vaginal anatomy requires primary excision for adequate evaluation of the tissue. With the currently available methods of evaluation and management of patients with VAIN, irradiation appears to have a limited role in the treatment of this disease.

#### REFERENCES

- DiSaia, P. J., Morrow, C. P., and Townsend, D. E.: Synopsis of Gynecologic Oncology, New York, 1975, John Wiley and Sons, p. 203.
- Geelhoed, G. W., Henson, D. E., Taylor, P. T., and Ketcham, A. S.: Carcinoma in situ of the vagina following treatment for carcinoma of the cervix: A distinctive clinical entity, Am. J. Obstet. Gynecol. 124:510, 1976.
- Lee, R. A., and Symmonds, R. E.: Recurrent carcinoma in-situ of the vagina in patients previously treated for in-situ carcinoma of the cervix, Obstet. Gynecol. 48:61, 1976.
- Cramer, D. W., and Cutler, S. J.: Incidence and histopathology of malignancies of the female genital organs in the United States, Am. J. OBSTET. GYNECOL. 118:443, 1974.
- Graham, J. B., and Meigs, J. V.: Recurrence of tumor after total hysterectomy for carcinoma in situ, Am. J. OBSTET. GYNECOL. 64:1159, 1952.
- Woodruff, J. D.: Treatment of recurrent carcinoma insitu in the lower genital canal, Clin. Obstet. Gynecol: 8:757, 1965.
- Parker, R. T., Cuyler, W. K., Kaufman, L. A., Carter, B., Thomas, W. L., Creadick, R. N., Turner, V. H., Peete, C. H., and Cherny, W. B.: Intraepithelial (Stage 0) cancer of the cervix, Am. J. Obstet. Gynecol. 80:693, 1960.
- 8. Gusberg, S. B., and Marshall, D.: Intraepithelial carcinoma of the cervix: A clinical reappraisal, Obstet. Gynecol. 19:713, 1962.
- Boyes, D. A., Worth, A. J., and Fidler, H. K.: The results of treatment of 4,389 cases of preclinical cervical squamous carcinoma, J. Obstet. Gynaecol. Br. Commonw. 77:769, 1970.
- Novak, E. R., and Woodruff, J. D.: Postirradiation malignancies of the pelvic organs, Am. J. Obstet. Gynecol. 77:667, 1959.
- 11. Taylor, E. S.: Discussion, in Rutledge, F.: Cancer of the vagina, Am. J. Obstet. Gynecol. 97:635, 1967.

- 12. Jordan, M. J.: Discussion, in Rutledge, F.: Cancer of the vagina, Am. J. Obstet. Gynecol. 97:635, 1967.
- Funnell, J. D., and Merrill, J. A.: Recurrence after treatment of carcinoma in-situ of the cervix, Surg. Gynecol. Obstet. 117:15, 1963.
- 14. Rutledge, F.: Cancer of the vagina, Am. J. Obstet. Gynecol. 97:635, 1967.
- 15. Guthrie, D., and Way, S.: Immunotherapy of non-clinical vaginal cancer, Lancet 2:1242, 1975.
- Gallup, D. G., and Morley, G. W.: Carcinoma in-situ of the vagina, Obstet. Gynecol. 46:334, 1975.
- Ferguson, J. H., and Maclure, J. G.: Intraepithelial carcinoma, dysplasia and exfoliation of cancer cells in the vaginal mucosa, Am. J. Obstet. Gynecol. 87:326, 1963.
- Hummer, W. K., Mussey, E., Decker, D. G., and Dockerty, M. B.: Carcinoma in-situ of the vagina, Am. J. Obstet. Gynecol. 108:1109, 1970.
- Gray, L. A., and Christopherson, W. M.: In-situ and early invasive carcinoma of the vagina, Obstet. Gynecol. 34: 226, 1969.
- Brown, G. R., Fletcher, G. H., and Rutledge, F. N.: Irradiation of "in-situ" and invasive squamous cell carcinomas of the vagina, Cancer 28:1278, 1971.
- Richart, R. M.: Natural history of cervical intraepithelial neoplasia, Clin. Obstet. Gynecol. 10:748, 1967.
- 22. Woodruff, J. D., Parmley, T. H., and Julian, C. G.: Topical 5-fluorouracil in the treatment of vaginal carcinoma in situ, Gynecol. Oncol. 3:124, 1975.
- 23. Usherwood, M. McD.: Management of vaginal carcinoma after hysterectomy, Am. J. Obstet. Gynecol. 122:352, 1975.
- 24. Newman, W., and Cromer, J. K.: The multicentric origin of carcinomas of the female anogenital tract, Surg. Gynecol. Obstet. 108:273, 1959.
- Marcus, S. L.: Multiple squamous cell carcinomas involving the cervix, vagina and vulva: The theory of multicentric origin, Am. J. Obstet. Gynecol. 80:802, 1960.

- Jimerson, G. K., and Merrill, J. A.: Multicentric squamous malignancy involving both cervix and vulva, Cancer 26:150, 1970.
- 27. Jimerson, G. K., and Merrill, J. A.: Cancer and dysplasia of the posthysterectomy vaginal cuff, Gynecol. Oncol. 4:328, 1976.
- 28. Copenhaver, E. H., Ferdinand, A. S., and Wright, K. A.: Carcinoma in-situ of the vagina, Am. J. Obstet. Gynecol. 89:962, 1964.
- 29. Briggs, R. M.: Dysplasia and early neoplasia of the uterine cervix. A review, Obstet. Gynecol. Surv. 34:70, 1979.
- 30. Levy, D. L., and Kelly, J. M.: Primary multifocal carcinoma in-situ of the vagina and vulva in a young woman, Am. J. Obster. Gynecol. 127:327, 1977.
- Palmer, J. P., and Spratt, D. W.: Pelvic carcinoma following irradiation for benign gynecologic diseases, Am. J. OBSTET. GYNECOL. 72:497, 1956.
- 32. Pride, G. L., and Buchler, D. A.: Carcinoma of vagina, 10 or more years following pelvic irradiation therapy, Am. J. OBSTET. GYNECOL. 127:513, 1977.
- 33. Koss, L. G., Stewart, F. W., Foote, F. W., Jordan, M. J., Bader, G. M., and Day, E.: Some histological aspects of behavior of epidermoid carcinoma in situ and related lesions of the uterine cervix, Cancer 16:1160, 1963.
- 34. Fu, Y. S., Reagan, J. W., Richart, R. M., and Townsend,

- D. E.: Nuclear DNA and histologic studies of genital lesions in DES-exposed progeny. I. Intraepithelial squamous abnormalities, Am. J. Clin. Pathol. 72:503, 1979.
- Jansen, G. T., Dillaha, C. J., and Honeycutt, W. M.: Bowenoid conditions of the skin: Treatment with topical 5-fluorouracil, South. Med. J. 60:185, 1967.
- 35. Ballon, S. C., Roberts, J. A., and Lagasse, L. D.: Topical 5-fluorouracil in the treatment of intraepithelial neoplasia of the vagina, Obstet. Gynecol. 54:163, 1979.
- 37. Bowen-Simpkins, P., and Hull, M. G. R.: Intraepithelial vaginal neoplasia following immunosuppressive therapy treated with topical 5-FU, Obstet. Gynecol. 46:360, 1975.
- 38. Huil, M. G. R., Bowen-Simpkins, P., and Paintin, D. B.: Topical treatment of vaginal intraepithelial neoplasia, Obstet. Gynecol. 49:382, 1977.
- Hull, M. G. R., Bowen-Simpkins, P., and Paintin, D. B.: 5-Fluorouracil versus immunotherapy for non-clinical vaginal cancer, Lancet 1:588, 1976.
- 4). Carter, R., Krantz, K. E., Hara, G. S., Lin, F., Masterson, B. J., and Smith, S. J.: Treatment of cervical intraepithelial neoplasia with the carbon dioxide laser beam, Am. J. Obstet. Gynecol. 131:831, 1978.
- 41. Stafl, A., Wilkinson, E. J., and Mattingly, R. F.: Laser treatment of cervical and vaginal neoplasia, Am. J. Obstet. Gynecol. 128:128, 1977.

### Granulosa cell tumors: A comparison of survival in patients and matched controls

ELISABET BJÖRKHOLM, M.D.

Stockholm, Sweden

The survival rate in a group of 153 patients with granulosa cell tumor of the ovary was compared to that in a control group of 306 women who were matched with respect to age and geographical location. The mean follow-up time was 15.0 years. The 5-year survival rate was 85% for the tumor group as compared to 98% for the controls. The mortality from all causes was 2.2 times greater for the tumor group. There was no excess mortality from endometrial or breast cancer. The mortality from cerebrovascular and cardiovascular diseases was greater for the tumor group.

(Am. J. Obstet. Gynecol. 138:329, 1980.)

THE PROGNOSIS for patients with granulosa cell tumor is much better than for women with malignant diseases of the ovary in general. For this tumor and the pure thecoma, the annual incidence in the Swedish female population was 1.60 per 100,000 for the period 1959-1965. Even so, a considerable number of women with granulosa cell tumor have been seen at Radiumhemmet over the years. Thanks to conditions that are highly favorable for tracing patients in Sweden, the outcome for nearly all patients is known. The population registration system enables age-matched and geographically matched controls to be obtained for all the patients living outside the City of Stockholm.

The purpose of this study was to compare the survival rates and the causes of death for a group of patients with granulosa cell tumor to those for a group of control women. This series would appear to be one of the largest gathered by a single hospital, and the patients have been followed for a long time.

It is well known that the risk of developing endometrial carcinoma is greater for women with feminizing ovarian tumors, most of them of the granulosa cell and theca cell types, than it is for the general female popu-

> From the Department of Gynecological Oncology, Radiumhemmet, Karolinska Hospital.

This study was supported by the Swedish Cancer Society and the King Gustaf V Jubilee Fund.

Received for publication December 28, 1979.

Revised April 17, 1980.

Accepted May 29, 1980.

Reprint requests: Elisabet Björkholm, M.D., Department of Gynecological Oncology, Radiumhemmet, Karolinska Hospital, S-104 01 Stockholm, Sweden. lation.<sup>3, 4</sup> Because of the ability of the granulosa cell tumor to produce estrogens, these women may have an elevated risk of death from causes other than the tumor itself.

An examination was also made of the causes of death in relation to the treatment for the disease—mostly, operation followed by external irradiation—with a view to establishing whether this might have a bearing on the death rate.

#### Material and methods

Patient series. During the 50 year period 1923-1972, a total of 253 women with histologically verified granulosa cell tumor was treated at Radiumhemmet. They came from practically the whole of Sweden, but because of the lack of controls for women living in the Stockholm area, these 100 patients were not included in the series, which thus ultimately numbered 153 cases.

The histologic classification was performed at the Department of Tumor Pathology at the time of admission. Reference was also made to the medical report. The patient data used in the study are presented in Table I.

Control group. To each of the 153 patients, two control women were assigned, a total of 306. They were chosen as being of the same age as the patient and residing in the same parish at the time of diagnosis. Since population registration is maintained on the parish level in Sweden, geographic matching was automatic. The control women were the persons having birth dates on each side of that of the patient. The birth data is part of the identification number assigned to each member of the population. These data were ob-

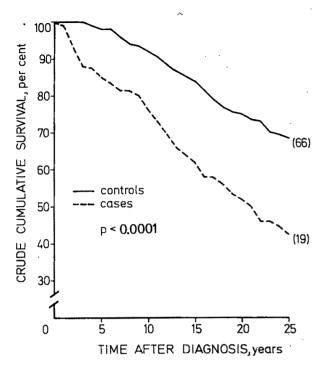


Fig. 1. Crude cumulative percentage of survivors. The numbers of patients and controls at entry were 153 and 306, respectively; the numbers still living and under observation after 25 years were 19 and 66.

**Table I.** Data used in the study, patient and control series

Date of birth
Place of residence
Date of entry into the study (diagnosis)
Date of last follow-up
Date of death
Cause of death

tained through the parish population registry for all of the patients residing outside the City of Stockholm. The data used are presented in Table I.

Follow-up examination. The follow-up of the patients and the controls was performed in 1977-1978, and a stop date of collecting this series was set to November, 1977. The population registry was used to ascertain whether the women were still living; if a patient had died, the date and cause of death, as entered on the death certificate, were obtained. Only one woman was lost to follow-up.

All deaths from granulosa cell tumor were verified either clinically or histologically.

Treatment. The treatment was fairly uniform. All the patients had had an operation—usually bilateral oophorectomy—and 87% of them had also had external irradiation. In some of the earlier cases, intrauterine radium therapy had also been given in order

to supplement the x-ray dose to the true pelvis. The high-voltage technique has been employed since the mid-1960's. At the time of the diagnosis, 4% of the women also had endometrial carcinoma, and they underwent preoperative intrauterine radium therapy prior to hysterectomy and salpingo-oophorectomy.

**Statistical methods.** All the data were punched on cards for statistical analysis.

The survival over time was described by using life tables, and differences in survival were studied by means of the log-rank test as described by Peto and co-workers.8

Person years at risk were calculated from the date the patients and controls had entered the study (the date of diagnosis in the former case) until the date of last follow-up or death. The relative risk of death from various causes is defined as the ratio of deaths among the patients to deaths among the controls, taking account of the person years at risk. A 95% two-tailed confidence interval was calculated for the relative risk.

#### Results

The mean follow-up time for the patients, reckoned from the diagnosis until death or the follow-up, was 15.0 years (range, 0 to 47 years). At the follow-up, 72 of the women were alive, and only 29 of them had been followed for less than 15 years. Four women had died of their tumors more than 20 years after the diagnosis, the longest interval being 30 years.

The mean ages of both the patients and the controls at entry were 53 years.

The crude cumulative percentage of survivors (counting deaths from all causes) for the 153 patients with granulosa cell tumor and the 306 controls is presented in Fig. 1. There was a statistically significant difference in survival between the patients and the controls, p < 0.0001. At 5 years, 85% of the women who comprised the tumor group were alive as compared to 98% of those in the control group.

The 153 patients were followed for 2,287 person years, and the 306 controls for 5,762 person years. Deaths among the patients from any cause numbered 80, as compared to 93 among the controls. Thus, the relative risk of death from any cause was 2.2 (95% two-tailed confidence interval [1.6, 3.0]). Even when the deaths from ovarian carcinoma were excluded, the risk of death was significantly higher in the patient group, with the relative risk for this subgroup being 1.5 (95% two-tailed confidence interval [1.1, 2.1]). Death in two patients was due to endometrial carcinoma, and in five, to breast cancer; the corresponding figures for the control group were 1 and 6. (There was no statistically significant difference by the chi-square test.) Leukemia

was not responsible for any deaths among the patients, but it did cause the deaths of three women in the control group. The excess difference in the death rate seems to have been due to cerebrovascular and cardiovascular diseases, with 29 deaths from these causes among the patients and 40 among the controls; the relative risk was 1.8 (95% two-tailed confidence interval [1.4, 2.3]).

#### Comment

The 5-year survival rate for the patients with granulosa cell tumor was consistent with the findings of other authors.9, 10 Deaths which occurred between 20 and 30 years after the initial diagnosis have also been reported in earlier series.2 However, whether such patients developed a new tumor of this type or a recurrence of the original one is uncertain. As in most other malignant diseases, the tumor mortality was fairly high shortly after the diagnosis; here, however, deaths from the tumor disease were still occurring up to 30 years after the diagnosis.

Although the causes of death in the subjects of this study are fairly well documented, because of having been obtained from the official statistics based on death certificates, the possibility of error cannot be ruled out, especially in regard to the information from early years. Apart from deaths due to granulosa cell tumor, the mortality from cerebrovascular and cardiovascular

diseases was also greater than that for the matched controls; possibly, this can be ascribed to a disturbance in hormonal balance, in view of the estrogen-secreting property of the tumor.6 On the other hand, the treatment which consists of oophorectomy and external irradiation, results in destruction of ovarian function. A special hormonal disposition in these women cannot be ruled out. In view of the high frequency of endometrial carcinoma among women who are suffering from feminizing ovarian tumors, the difference, or rather the absence of any difference, between patients and controls in mortality from endometrial carcinoma is of special interest. It should be borne in mind that most of the endometrial carcinomas were well differentiated. Some investigators who doubt that these lesions are malignant claim that most of those which occur in patients with granulosa cell tumors are, in fact, hyperplasias arising from hormonal stimulation.<sup>5</sup>

Although most of the patients received radiotherapy, no deaths from leukemia were reported.

This study shows that granulosa cell tumors can display highly malignant behavior, and the death rate due to them is greatest during the first 2 years after the diagnosis. Curiously enough, deaths from this kind of tumor can occur as long as 30 years after diagnosis.

I wish to thank Mr. Bo Nilsson for valuable help with the statistical calculations.

#### REFERENCES

- 1. Axelson, O., and Ulander, A.: Epidemiologi, efter föreläsningar av O.S. Miettinen, 1975, Yrkesmedicinska kliniken, Regionsjukhuset i Örebro och Arbetarskyddsfonden, pp. 68-74. (In Swedish.)
- 2. Diddle, Â. W.: Granulosa- and theca-cell ovarian tumors: Prognosis, Cancer 5:215, 1952.
- 3. Greene, J. W., Jr.,: Feminizing mesenchymomas (granulosa-cell and theca-cell tumors) with associated endometrial carcinoma, Am. J. Obstet. Gynecol. 74:31, 1957.
- 4. Gusberg, S. B., and Kardon, P.: Proliferative endometrial response to theca-granulosa cell tumors, Am. J. OBSTET. GYNECOL. 111:633, 1971.
- 5. Ingraham, C. B., Black, W. C., and Rutledge, E. K.: The relationship of granulosa-cell tumors of the ovary to endometrial carcinoma, Am. J. OBSTET. GYNECOL. 48:760,
- 6. Kurman, R. J., Goebelsmann, U., and Taylor, C. R.: Ste-

- roid localization in granulosa-theca tumors of the cvary, Cancer 43:2377, 1979.
- 7. National Board of Health and Welfare, The Cancer Registry: Cancer Incidence in Sweden, 1959-1965, Stockholm, 1971, National Board of Health and Welfare, p. 34.
- 8. Peto, R., Pike, M. C., Armitage, P., Breslow, N. E., Cox, D. R., Howard, S. V., Mantel, N., McPherson, K., Peto, J., and Smith, P. G.: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples, Br. J. Cancer 35:1, 1977.
- 9. Sjöstedt, S., and Wahlén, T.: Prognosis of granulosa cell tumors, Acta Obstet. Gynecol. Scand. (Suppl. 6) 40:3, 1961.
- 10. Stenwig, J. T., Hazekamp, J. T., and Beecham, J. B.: Granulosa cell tumors of the ovary. A clinicopathological study of 118 cases with long-term follow-up, Gynecol. Oncol. 7:136, 1979.

#### Evidence for a human ovarian progesterone receptor

BARRY R. JACOBS, M.D. SUSAN SUCHOCKI ROY G. SMITH, Ph.D. Houston, Texas

The aromatization of androgens to estrogens in the ovary and the roles of estrogens in promoting follicular growth have been described by a number of investigators. Furthermore, specific receptors for estrogens have been defined in granulosa cells as well as other target tissues. In other estrogen-responsive tissues, there is also a progesterone receptor, which mediates estrogen antagonism at the molecular level. We have previously described an ovarian progesterone receptor in an animal model. We now describe a heat-labile ovarian cytoplasmic protein that specifically binds progestins with a very high affinity. The equilibrium dissociation constant for progesterone (Kd) = 4.8 × 10<sup>-9</sup>M and it is present in the ovary in a concentration of 3.3 × 10<sup>-13</sup> moles/mg of protein. Since the characteristics of this protein are compatible with an ovarian progesterone receptor, there is the implication that the ovary is a target organ for progesterone. Thus, progesterone may have a role in the modulation of ovarian physiology. (Am. J. Obstet. Gynecol. 138:332, 1980.)

THE MODULATION of ovarian physiology by steroid hormones had been discussed by a number of investigators. Goldenberg and associates¹ found that estrogens stimulate follicular growth and Richards and colleagues² described the increased binding of folliclestimulating hormone (FSH) to granulosa cells stimulated by estrogens. This increased binding of FSH is accompanied by an increase in the aromatization of testosterone (T) to estradiol.² These effects of estrogen on granulosa cells are probably mediated by ovarian estrogen receptors such as those characterized by Scott and Rennie³ and Richards.⁴ Therefore, there exists in the ovary a positive feedback of estrogen.

In every biologic system studied, there is a negative feedback for each positive one. In the uterus progesterone (P) provides this opposition to estrogen. P decreases the replenishment of estrogen receptors<sup>5</sup> and increases the metabolism of the potent estradiol- $17\beta$  (E<sub>2</sub>) to the less potent estrone.<sup>5</sup> Is there a similar

From the Department of Obstetrics and Gynecology and the Laboratory of Molecular Endocrinology, Division of Urology, Department of Surgery, The University of Texas Medical School at Houston.

Received for publication January 4, 1980. Revised April 28, 1980.

Accepted May 29, 1980.

Reprint requests: Barry Jacobs, M.D., Department of Obstetrics and Gynecology, The University of Texas Medical School at Houston, 643 J. Fannin, Suite 3270, Houston, Texas 77030. P-mediated phenomenon in the ovary? The first step in answering this question is to determine if there is an evarian P receptor. Such a protein was first described by us in the calf.<sup>6</sup> In an effort to determine if there is a similar protein in the human, the experiments described in this communication were performed.

#### Material and methods

All chemicals and solvents were reagent or analytical grade and were obtained from commercial suppliers. Ribonuclease A (bovine pancreas), deoxyribonuclease II, trypsin (Type III), and pronase (from Streptomyces griseus) were obtained from Sigma Chemical Co. Unlabeled steroids, P, T, dihydrotestosterone (DHT), E<sub>2</sub>, cortisol (F), and diethylstilbestrol (DES) were obtained from Steraloids, Inc. Tritiated steroids, P (<sup>3</sup>H-P) and R5020 (<sup>3</sup>H-R5020), as well as unlabeled R5020 were obtained from New England Nuclear.

Ovaries were obtained from premenopausal gynecologic patients undergoing pelvic laparotomy for adnexectomy, either associated with hysterectomy or after hysterectomy. There was no selection on the basis of phase of the menstrual cycle and none of these patients was under the care of the investigators. All procedures were performed for medical indications (e.g., residual ovary syndrome, pelvic inflammatory disease, and ectopic pregnancy). Tissue obtained in the operating room was immediately immersed in saline at 0° C and transported to the pathologist. After his evaluation of the ovaries, they were transported to the research laboratory. All tissue preparations and incubations were performed at 4° C. The tissue was minced with knife and scissors. Each gram of tissue was then homogenized in 4 ml of buffer (10 mM tris (hydroxymethyl) methylamine-hydrochloride, pH 7.4, ethylenediaminetetra-acetate, 12 mM 1.5 mM thioglycerol, and 10% glycerol) with the use of 10second bursts of a TissueMizer (Tekmar). The resulting homogenate was centrifuged at 800 × g for 20 minutes in a Sorvall RC-5B centrifuge. The resulting supernatant was centrifuged at 200,000 × g for 1 hour in a Sorvall OTD 65 ultracentrifuge with an AH 650 rotor. Endogenous steroids were removed with an equal volume of a dextran-charcoal suspension in the same buffer. After a 1-hour incubation, the charcoal was removed from the suspension by centrifugation at 800 × g for 10 minutes. The resulting cytosol was used in the experiments described.

All assays were performed with approximately 6 nM tritiated steroid. Cortisol (10<sup>-7</sup>M) was added to the cytosol prior to all studies. This was done to prevent binding of <sup>3</sup>H-P to cortisol-binding globulin (CBG). Scatchard analysis of binding<sup>7</sup> was performed with a 100-fold excess of unlabeled steroid to displace specific binding of tritiated steroid in a concentration range of 0.4 to 12 nM. Competition curves were performed with the use of competitors in a concentration range of 500 pM to 1 uM. Incubations were at 4° C overnight. Ur.bound steroid was removed from the incubation solutions after a 5-minute exposure to 0.5 ml of the dextran-charcoal suspension described above. The charcoal was removed by centrifugation at 800 × g for 10 minutes in the Sorvall RC-5B.

Under the incubation conditions described above macromolecular bound tritiated steroid to be chromatographed was extracted three times with five volumes of anhydrous ether. This removed more than 98% of the labeled steroid. After the ether was evaporated under nitrogen, the residue was redissolved in benzene: methylene chloride (1:1) and spotted on thin-layer silica gel sheets (Eastman). Thin-layer chromatography was performed according to the method described by Strott<sup>8</sup> to separate P from its metabolites. Pure preparations of P,  $5\alpha$ -pregnane-3,20-dione, and 4-pregnen-20 $\beta$ -ol-3-one were chromatographed simultaneously as references.

Sucrose density gradients (5% to 25%) were made with a Beckman density gradient former. After incubation with 3H-R5020, unbound steroid was removed from cytosol with charcoal. Then 200  $\mu$ l of cytosol labeled with <sup>3</sup>H-R5020 and 40 µl of ovalbumin (Svedberg coefficient [S] = 3.7) and yeast alcohol dehydrogenase (\$ = 7.6) which had been labeled with <sup>14</sup>C were layered on the gradients. The 14C-labeled proteins served as

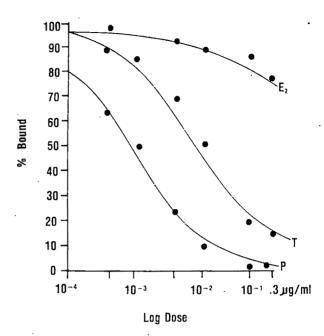


Fig. 1. Competition curves comparing displacement of <sup>3</sup>H-P by the naturally occurring potent sex steroids P, T, and E2 demonstrate relative binding affinities of the macromolecule for these hormones. The results of the binding assays are displayed as percent bound versus the natural log of the concentration of the competing steroid in micrograms per milliliter over a concentration range of approximately 500 pM to 1 µM. The curves were drawr, with the aid of a computer according to the program of Rodbard and associates. 10

Table I. Results of competitive binding assays

	Percent displacen	nent by competitor
Competitor	Fiftyfold excess	100-Fold excess
P	100	100
$\mathbf{E_2}$	$13.9 \pm 3.9$	$22.6 \pm 0.05$
DES	<<0.5	$3.4 \pm 2.2$
DHT	$25.5 \pm 2.8$	$40.3 \pm 0.5$
T	$45.3 \pm 3.8$	$60.1 \pm 1.3$

sedimentation markers. Gradients were centrifuged at 200,000 × g for 2\% hours in the OTD 65 ultracentrifuge with a TV 865 vertical rotor. Enzyme degradation studies were performed in a constant-temperature water bath at 37 C for 30 minutes. Heat-stability studies were performed at 37° C for 1 hour. After these incubations, the assay tubes were immediately transferred to an ice slush and the remainder of the assay was performed at 4° C. Enzyme degradation studies were performed in the presence of P and R5020 and a 10 μg/ml concentration of trypsin, pronase, ribonuclease (RNase) or deoxyribonuclease (DNase).

Tritium disintegrations were counted in a Packard Tri-Carb liquid-scintillation counter with 7 ml of Scintiverse (Fisher) used as a cocktail. Counting efficiency was 25%. Protein determinations were performed as:

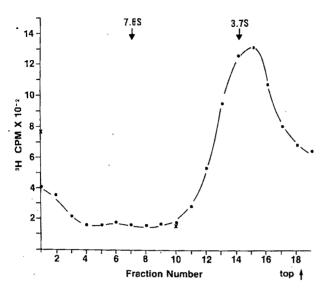


Fig. 2. Sucrose density gradients (5% to 25%), were centrifuged in a vertical rotor at  $200,000 \times g$  for 2% hours. The fractions of each gradient contained a single peak of macromolecular bound tritiated progestin. Ovalbumin (S = 3.7) and yeast alcohol dehydrogenase (S = 7.6) were labeled with  $^{14}$ C.

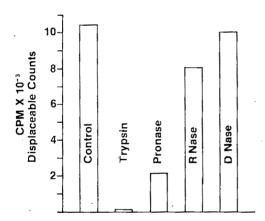


Fig. 3. Cytosol preparations and progestin were incubated at 37° C for 30 minutes. The enzymes trypsin, pronase, RNase, and DNase were evaluated to determine their ability to interfere with binding of <sup>3</sup>H-P.

described by Bradford<sup>9</sup> by reacting soluble protein with Coomassie Blue. Bovine serum albumin was used to establish the standard curve.

#### Results

Competive binding assays were initially performed with the use of a fiftyfold and a 100-fold excess of competitors in the presence of F. The results, given in Table I, show that displacement of  ${}^3H$ -P is significantly greater by P than by any of the other hormones (n = 3). These data are expressed as the mean  $\pm$  SD. The capacity of each competitor to inhibit  ${}^3H$ -P binding is expressed relative to the displacement of  ${}^3H$ -P by

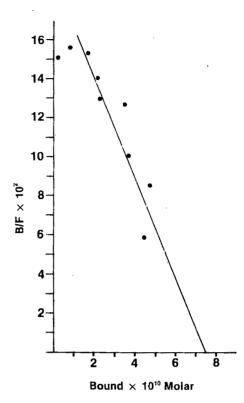


Fig. 4. Ovarian cytosol was incubated with  $^3$ H-R5020 over a concentration range of 0.4 to 12 nM. Identical incubations were performed with a 100-fold excess of radioinert R5020 to determine nonspecific binding. The affinity of binding was cetermined by Scatchard analysis. Kd = 1.9 nM, and the concentration of binding sites was  $3.3 \times 10^{-13}$  moles/mg of protein.

radioinert P. P is used here as a standard and assigned a value of 100%. Since F was added (concentration = 100 nM) to each of the incubation tubes prior to the addition of other hormones, no competition for <sup>3</sup>H-P displacement by F is shown since it is negligible or nonexistent.

Further and more complete studies of the characteristics of competition for <sup>3</sup>H-P binding by naturally occurring potent sex steroids in the human are graphed in the competition curves shown in Fig. 1. The data are expressed in terms of percent bound versus the natural og of the dose of each of the competitors, P, E<sub>2</sub>, and T. The curves were plotted by a Wang Model 2200 computer by means of the technique described by Rodbard and associates <sup>10</sup> for establishing curves for radioimmunoassays. To achieve 50% displacement of <sup>3</sup>H-P by T requires approximately 120 times as much T as P. Also note that E<sub>2</sub> displaces only a minimal percentage of the <sup>3</sup>H-P and then only at very high concentrations.

For analysis of receptors by sucrose gradient centrifugation, R5020 was used as the ligand since it dissociates more slowly from the receptor than P.<sup>11</sup> The otilization of a vertical rotor significantly decreased the

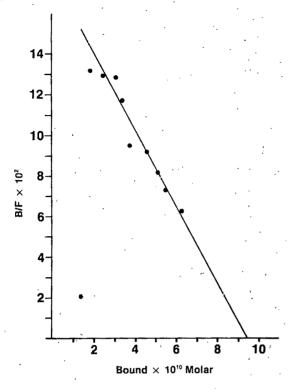


Fig. 5. Similar incubations to those in Fig. 4 with <sup>3</sup>H-P used as the ligand and radioinert P used as the competitor were performed. Scatchard analysis of binding of <sup>3</sup>H-P demonstrates a Kd = 4.8 nM and a concentration of binding sites similar to those of R5020.

centrifugation time, which further minimized dissociation of radiolabeled steroid from protein. The result of this technique was a single band of specially bound radioactivity. This migrated with an  $S=3.5\pm0.2$  (n = 4). Comparable values were found when P was used as a ligand but a small peak of radioactivity was noted near the top of the gradient under these conditions, implying a detectable amount of dissociation even in the relatively short centrifugation. A representative sucrose gradient is shown in Fig. 2.

Similar to our previously described finding in the bovine ovary, 6 the binding of progestin is to a heatlabile protein. Incubation of the cytosol without steroid in a 37° C water bath for 1 hour destroyed over half the specific binding of R5020 but the presence of progestin in the incubation mixture apparently somewhat protected the macromolecule. Enzyme degradation studies demonstrated a marked diminution of specific binding by the proteolytic enzymes pronase and trypsin but not by RNase or DNase (Fig. 3). The modest decrease in binding effected by RNase may be the result of contamination of the enzyme by a proteolytic enzyme.

Scatchard analysis of  $^3$ H-R5020 binding, as shown in Fig. 4, revealed a single binding component with an equilibrium dissociation constant (Kd) =  $1.9 \pm 1.2 \times$ 

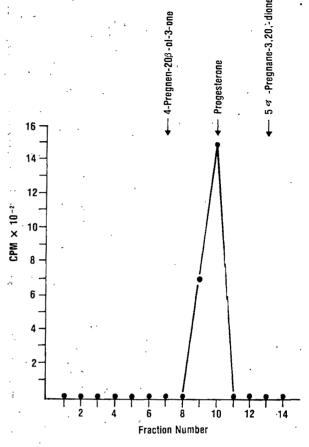


Fig. 6. After incubation of  ${}^{3}\text{H-P}$  with ovarian cytosol, free steroid was removed by dextran/charcoal. Macromolecular bound steroid was then extracted with anhydrous ether. The residue remaining after evaporation of the ether was chromatographed on thin-layer gels. Authentic standards of 4-pregnen-20 $\beta$ -ol-3-one, progesterone, and  $5\alpha$ -pregnane-3,20,-dione were used as reference standards. Both nonspecific binding and total binding were evaluated. The mathematical difference between these is the displaceable binding plotted.

 $10^{-9}$ M when determined over a concentration range of 0.5 to 10 nM. The apparent concentration (C) =  $330 \pm 35$  fmoles/mg of protein (n = 5). Binding of P was also of high affinity (Fig. 5)—Kd =  $4.8 \pm 2.9 \times 10^{-9}$ M—and the number of binding sites was similar to that of R5020 (n = 5). The Kd of this protein represents a high affinity for progestins under the equilibrium conditions described.

Thin-layer chromatography (n = 3) of specifically bound tritiated P demonstrate a single peak of radioactivity which migrated with the authentic progesterone standard (Fig. 6). This implies that all of the bound steroid is probably P and any metabolism of the critiated hormone is not apparent in the binding studes. This differs slightly from our findings in bovine ovarian cytosols which apparently metabolized approxmately 20% of the <sup>3</sup>H-P.<sup>8</sup> More important, however, is

that progesterone itself is bound with very high affinity to a cytoplasmic protein.

#### Comment

The P-binding protein described in this communication has characteristics of a P receptor. It is of high affinity and limited capacity. The protein's affinity for progestins is highly specific and the fact that it binds R5020 even in the presence of excess cortisol is further evidence that it is a P receptor. The Svedberg sedimentation coefficient, as estimated by the sucrose gradient studies, is compatible with those which have been reported previously. 6. 12. 13 Although both 4S and 8S progesterone receptors have been described, the single 3.6S component described in this communication is consistent with our previous observations in the animal model system<sup>6</sup> and is similar to that described for the purified P receptor isolated from the human uterus.14 The results of thin-layer chromatography on the ether extract of the steroid bound to the receptor demonstrate that P itself is bound and is not a metabolite such. as  $5\alpha$ -dihydroprogesterone. Because the experiments discussed here were performed on human tissues, it was not possible to demonstrate tissue specificity with the classic nontarget tissues, the spleen, lung, or heart, from the same patient.

The ovaries used in the experiments described in this communication were removed for a variety of reasons. All of the patients were in the reproductive age range and had active follicles. Some had had a previous hysterectomy and it was not possible to date the stage of the menstrual cycle at the time of operation. In those women having hysterectomy with adnexectomy, the time of the cycle was noted. In contrast to our findings in the bovine ovary, specific progesterone binding was noted in both the follicular and luteal phases. The number of assays in each phase is too small to identify a significant difference in the concentration of binding when the two phases of the cycle are compared.

This is the first description of a putative human ovarian P receptor. Until a biological response has been associated with the interaction of P with this P-specific ovarian binding protein it cannot be strictly termed a receptor. Still to be performed are studies to determine the exact action of P on ovarian physiology. Goodman and Hodgen<sup>15</sup> found that there is apparently a direct inhibitory effect of progesterone on follicular growth. Cunningham and associates<sup>16</sup> described an inhibition of ovulation by another steroid known to be bound by P receptors. These findings imply that the ovary is a target organ for P and that P may be the negative feedback for follicular growth.

#### REFERENCES

 Goldenberg, R. L., Vaitukaitis, J. L., and Ross, G. T.: Estrogen and follicle stimulating hormone interactions of follicle growth in rats, Endocrinology 90:1492, 1972.

Richards, J., Uilenbroek, J. Th. J., and Jonassen, J. A.:
Follicular growth in the rat: A reevaluation of the roles of
FSH and LH, in Channing, C. P., March, J., and Sadler,
W. A., editors: Ovarian Follicular Growth and Corpus
Luteum Function, New York, 1979, Plenum Publishing
Corporation, p. 11.

 Scott, R. S., and Rennie, P. I. C.: An estrogen receptor in the corpus luteum of the pseudopregnant rabbit, Endocrinology 89:297, 1971.

 Richards, J. S.: Content of nuclear estradiol complex in rat corpora lutea during pregnancy—relationship to estrogen concentration and cytosol receptor availability, Endocrinology 96:227, 1975.

Tseng, L., Gusberg, S. B., and Gurpide, E.: Estradiol receptor and 17β-dehydrogenase in normal and abnormal endometrium, Ann. N. Y. Acad. Sci. 286:190, 1977.

- Jacobs, B. R., and Smith, R. G.: Evidence for a receptorlike protein for progesterone in bovine ovarian cytosol Endocrinology 106:1276, 1980.
- 7. Scatchard, G.: The attractions of proteins for small molecules and ions, Ann. N. Y. Acad. Sci. 51:560, 1949.
- Strott, C. A.: Metabolism of progesterone in the chick oviduct—relationship to progesterone receptor and biologic activity, Endocrinology, 95:825, 1974.
- 9. Bradford, M. M.: A rapid and sensitive method for quantitation of microgram quantities of protein utilizing the

- principle of protein-dye-binding, Anal. Biochem. 72:248, 1976.
- Rodbard, D., Rayford, P. L., Cooper, J. A., and Ross, G. T.: Statistical quality control of radioimmunoassays, J. Clin. Endocrinol. Metab. 28:1412, 1968.
- Raynaud, J. P.: R5020, A tag for the progestin receptor, in McGuire, W. L., Raynaud, J. P., and Baulieu, E. E., editors: Progesterone Receptors in Normal and Neoplastic Tissues, New York, 1977, Rayen Press, p. 9.
- Kontula, K., Janne, O., Luukkainen, T., and Vihko, R.: Progesterone binding in human myometrium. Ligand specificity and some physicochemical characteristics, Biochim. Biophys. Acta 328:145, 1973.
- 13. Young, P. C. M., and Cleary, R. E.: Characterization and properties of progesterone binding components in human endometrium. J. Clin. Endocrinol. Metab. 39:425, 1974.
- 14. Smith, R. G., Iramain, C. A., Buttram, V. C., and O'Malley, B. W.: Purification of human uterine progesterone receptor, Nature 253:271, 1975.
- Goodman, A. L., and Hodgen, G. D.: Systemic versus intraovarian progesterone replacement after luteectomy in rhesus monkeys: Differential patterns of gonadotropins and follicle growth, J. Clin. Endocrinol. Metab. 45:837, 1977.
- Cunningham, G., Goldzieher, J., de la Pena, A., and Oliver, M.: Mechanisms of ovulation inhibitions by triamcinolone acetonide, J. Clin. Endocrinol. Metab. 46:8, 1978.

#### Relaxation of human female genital sphincters by the neuropeptide vasoactive intestinal polypeptide

B. WALLES, PH.D.

R. HÅKANSON, PH.D.

G. HELM, M.D.

CH. OWMAN, M.D., PH.D.

N.-O. SJÖBERG, M.D., PH.D.

F. SUNDLER, PH.D.

Lund, Sweden

Vasoactive intestinal polypeptide (VIP), a recently recognized neuropeptide with a putative transmitter function, has been demonstrated in nerves in the female genital tract. The highest density is in the smooth muscle of the isthmus of the fallopiar tubes and of the uterine cervix. The motor effect of VIP has been tested in vitro on smooth muscle from the isthmus and the uterine cervix. Both preparations responded to VIP with a concentration-dependent reduction in motor activity. (Am. J. Obstet. Gynecol. 138:367, 1980.)

VASOACTIVE intestinal polypeptide (VIP) is one of a number of recently recognized neuropeptides, among which are also substance P, somatostatin, and enkephalin. They have all been demonstrated in the brain, as well as in nerves of peripheral organs.1 In the periphery, most of the peptide-containing nerves probably belong to the autonomic nervous system, although they seem to be distinct from adrenergic and cholinergic nerves. Since the recognized neuropeptides are contained in synaptic vesicles and have potent biologic actions, the assumption has been that they function as transmitters. Admittedly, the evidence for such a role is still incomplete. VIP nerves are numerous in the male and female genitourinary tract of several mammals.2 In human female genital organs, such nerves are comparatively numerous in the smooth muscle of the isthmic part of the fallopian tubes and of the uterine cervix.3 Data from radioimmunologic determinations of VIP support the microscopic observations.4

From the Departments of Histology, Pharmacology, and Obstetrics and Gynecology, University of Lund.

This work was supported by the Ford Foundation and the Swedish Medical Research Council (04X-4499).

Received for publication October 4, 1979.

Revised May 28, 1980.

Accepted May 29, 1980.

Reprint requests: Göran Helm, M.D., Department of Obstetrics and Gynecology, University Hospital, S-221 85 Lund, Sweden.

There are reasons to assume that nonadrenergic, noncholinergic nerves may be involved in the control of the tubal and cervical sphincters: first, the presence of "p-type" nerve terminals, which are ultrastructurally distinct from adrenergic and cholinergic ones,<sup>5</sup> and second, the finding that the electrically induced relaxation of smooth muscle strips from the tubal isthmus is only partly blocked by adrenergic or cholinergic antagonists.<sup>6</sup>

We have tested the motor effects of purified porcine VIP (a gift from Professor V. Mutt, Karolinska Institute, Stockholm, Sweden) on preparations of smooth muscle from the isthmus of the fallopian tubes and the uterine cervix, obtained at operations performed because of myoma or adenomyosis of the uterus. Only tissue that had a normal appearance was used. The 13 patients were 40 to 50 years old, received no hormone treatment, and were menstruating normally. The preparations were mounted in an aerated, temperature-controlled organ bath that contained Krebs-Ringer solution and were oriented so that the motor activity of either the longitudinal or the circular smooth muscle was primarily recorded.

The preparations from the tubes and cervix invariably showed spontaneous contractile activity, which was more regular in the tube (Fig. 1, A) than in the cervix (Fig. 1, B). VIP (dissolved in 0.9% saline solution) was added to the organ bath in cumulative doses that gave a final concentration from 1.25 to 250 ng/ml. Eleven



Fig. 1. Effect of VIP (25 ng/ml) on spontaneous contractile activity of the tubal isthmus (A) and uterine cervix (B). Horizontal bar, 1 minute; vertical bar, 500 dynes. Note that the effect of VIP was not immediate, possibly reflecting diffusion barriers in the preparations.

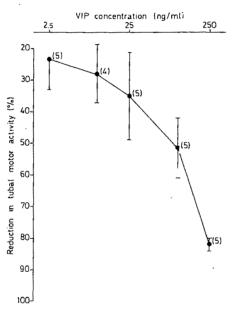


Fig. 2. Reduced contractile activity of the tubal isthmus in response to the stepwise addition of increasing doses of VI?. The final concentration in the bath is given. Similar results were obtained with smooth muscle from the cervix. Vertical bars gives the standard error of the mean. Number of observations in parentheses.

preparations of longitudinal smooth muscle and six preparations of circular muscle from the tubal isthmus all showed a dose-dependent reduction in spontaneous motor activity (measured planimetrically as the area under the curve in relation to the baseline during the 3 minute period of maximal effects, as compared to the same period of time immediately before addition of the drug) (Fig. 2). An effect was sometimes already recorded at the lowest dose tested; the highest dose almost completely suppressed motor activity, with only small isolated spikes remaining. The patterns of response were similar in both longitudinal and circular smooth muscle.

There were nine preparations of circular smooth muscle and seven of longitudinal muscle from the cervix. Administration of VIP caused relaxation similar to that seen with preparations from the tubal isthmus (Fig. 1, B).

In conclusion, since VIP occurs in nerve terminals in the smooth muscle of the isthmus and cervix, and since VIP is a potent relaxant of these anticipated sphincters, there are reasons to believe that neuronal VIP may be responsible for the nonadrenergic, noncholinergic relaxation induced by electrical stimulation of nerves.

#### REFERENCES

- 1. Pearse, A. G. E.: Peptides in brain and intestines, Nature (Lond.) 262:92, 1976.
- Alm, P., Alumets, J., Håkanson, R., and Sundler, F.: Feptidergic (vasoactive intestinal peptide) nerves in the genitourinary tract, Neuroscience 2:751, 1977.
- 3. Alm, P., Alumets, J., Håkanson, R., Helm, G., Owman, Ch., Sjöberg, N.-O., and Sundler, F.: Vasoactive intestinal polypeptide nerves in the human female genital tract, Am. J. Obstet. Gynecol. 136:349, 1980.
- 4. Helm, G., Ottesen, B., Fahrenkrug, J., Larsen, J.-J., Owman, Ch., Sjöberg, N.-O., Stolberg, B., Sundler, F. and
- Walles, B.: Vasoactive intestinal polypeptide (VIP) in human female reproductive tract: Distribution and motor effects. To be published, 1980.
- Sporrong, B., Clase, L., Owman, Ch., and Sjöberg, N.-O.: Electron microscopy of adrenergic, cholinergic, and "ptype" nerves in the myometrium and a special kind of synaptic contacts with the smooth muscle cells, Am. J. Obstet. Gynecol. 127:811, 1977.
- 6. Helm, G., Owman, Ch., Sjöberg, N.-O., and Walles, B.: Motor response of the human fallopian tube to electrical transmural nerve stimulation. To be published, 1980.

# The double uterus associated with an obstructed hemivagina and ipsilateral renal agenesis

JOHN A. ROCK, M.D.

HOWARD W. JONES, JR., M.D.\*

Baltimore, Maryland

Twelve patients with a double uterus, unilateral vaginal obstruction, and ipsilateral renal agenesis are described. The clinical presentation varies, depending on whether the obstruction was partial or complete. In rare instances a communication existed between the obstructed vaginal pouch and the opposite patent vagina through a defect in the septum of the double uterus. Early accurate diagnosis followed by the excision of the obstructing vaginal septum offers complete relief of symptoms while preserving reproductive capacity. (AM. J. OESTET. GYNECOL. 138:339, 1980.)

THE UNIQUE CLINICAL SYNDROME of the double uterus, a unilateral partially or completely obstructed vagina, and ipsilateral renal aplasia is quite rare. The clinical presentation varies, depending on the uterovaginal relationships which may obscure the true diagnosis. In the present report the anatomic variations and the associated symptoms in 12 patients are presented.

#### Material and methods

The present series consists of a historical prospective analysis of 12 patients evaluated by the authors in the Department of Gynecology and Obstetrics of The Johns Hopkins Hospital from January 1, 1950, to December 31, 1979. A careful review of patient histories, hysterograms, and operative notes allowed categorization of patients. The 12 patients were divided into three groups based on anatomic findings (Fig. 1).

In each patient a complete history was obtained and physical examination was performed. Laboratory evaluation consisted of a chemistry profile, urinalysis, and blood count, including determination of erythrocyte sedimentation rate. An intravenous pyelogram was ob-

> From the Division of Reproductive Endocrinology and Infertility, Section of Reproductive Surgery, The Johns Hopkins Hospital.

Received for publication January 16, 1980.

Revised April 11, 1980.

Accepted May 15, 1980.

Reprint requests: John A. Rock, M.D., Division of Reproductive Endocrinology and Infertility, Section of Reproductive Surgery, The Johns Hopkins Hospital, Baltimore, Maryland 21205.

\*Present address: Director of Gynecologic Oncology, Department of Obstetrics and Gynecology, Vanderbilt University, Nashville, Tennessee 37232.

tained in each patient for evaluation of renal status, and a vaginogram and a hysterosalpingogram were obtained for study of the details of the anomaly.

#### Results

Patient profile. A review of the literature revealed 71 patients described in two previous reports,<sup>2, 3</sup> with additional patients not included in those reports.<sup>4–6</sup> A review of these cases served as a reference to which the present series was compared (Table I).

The mean age at diagnosis was similar in both groups. The mean delay from first symptoms to diagnosis was 4.1 years in our patients. Without exception, each patient had congenital absence of the kidney on the side of the vaginal anomaly. This was observed on the right side in greater frequency than on the left.

Uterus didelphys was more commonly observed although a bicornuate or septate uterus was documented in a few instances.

#### Patient categorization.

Group 1: Complete vaginal obstruction with a hematocolpis. S x patients presented with a uterus didelphys and unilateral complete vaginal obstruction without uterine communication (Table II, Fig. 1, A). All patients presented with a paravaginal mass, severe dysmenorrhea, and lower abdominal pain. These patients reported progressively severe dysmenorrhea from menarche. An intermittent lower abdominal ache between menses usually was noted 1 to 2 years after menarche. All patients reported regular menses and one patient had premenstrual spotting. An intravenous pyelogram showed renal agenesis on the obstructed side in all

Complete relief of symptoms was observed after evacuat on of the hematocolpos and excision of the vag-

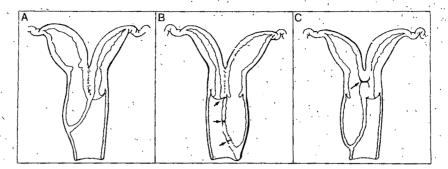


Fig. 1. Illustration of a double uterus, complete or incomplete vaginal obstruction, and ipsilateral renal agenesis. A: Complete vaginal obstruction. B: Incomplete vaginal obstruction C: Complete vaginal obstruction with a laterally communicating double uterus.

**Table I.** Profile of patients with a double uterus, unilateral vaginal obstruction, and ipsilateral renal agenesis

	Literature review	Present series	Total
Patients	71	12	83
Age:			
Range	11-43	-13-24	11-43
Mean	19	18	18
Renal agenesis:			• •
Right	31	8	39
Left	15	4	19
ND	25	0	25
Uterus:			
Didelphys	34	10	44
Double (type unknown).	21	. 0	21
Bicornuate	11	2	13
Septate	. 2	0.	2
ND	3	0	2 3

ND: Not determined.

inal septum. Four patients had term pregnancies after operation. Follow-up of one patient is incomplete, and one patient is not attempting to conceive.

Histopathologic examination of the removed septa showed normal squamous epithelium on the unobstructed side but columnar epithelium on the obstructed side.

Postoperatively, the exposed columnar epithelium gradually converted to squamous epithelium by metaplasia; however, 5 or more years were required for completion of the process.

Group 2: Incomplete vaginal obstruction without a hemato-colpos. Four patients were found to have incomplete unilateral vaginal obstruction without lateral uterine communication (Table II, Fig. 1, B). These patients presented with lower abdominal pain and moderate to severe dysmenorrhea. Without exception, each patient reported intermittent, foul, mucopurulent discharge. Furthermore, each patient reported a history of poly-

menorrhea with unpredictable staining between menstrual cycles. Each patient had a double uterus. An ill-defined paravaginal mass was noted in two patients. When the vagina was examined carefully, an opening in the partially obstructed vaginal pouch could be demonstrated with a fine metal probe. This was demonstrated to be adjacent to the cervix in one patient. The other patients were noted to have a defect at different points along the septal wall through which mucopurulent material extruded (Fig. 1, B). An intravenous pyelogram snowed renal agenesis on the partially obstructed side in all cases.

Histopathologic examination of the excised septa showed normal squamous epithelium on both sides of the septa.

Group 3: Complete vaginal obstruction with a laterally communicating double uterus. Two patients had complete vaginal obstruction with a laterally communicating double uterus (Table II, Fig. 1, C). Each patient had an intermittent irregular vaginal mass and dysmenorrhea. One patient complained of excessive, foul, mucopurulent discharge. Both patients reported regular menses. Each patient had a bicornuate uterus and intravenous pyelogram showed renal agenesis on the obstructed side.

Surgical treatment consisted of the excision of the vaginal septum. One patient had a term pregnancy; the other is not trying to conceive.

Histopathologic examination of one of the two septa showed squamous epithelium on the unobstructed side and columnar epithelium on the obstructed side. The histologic section of the other septum in this small group was not available for examination.

Surgical reconstruction. Excision of the vaginal septum is the procedure of choice for the surgical correction of the anomaly. The vaginal pouch is opened and the blood or mucus removed by suction and lavage. The obstructing septum is usually thick, and removal

Table II. Patients with a double uterus associated with unilateral vaginal obstruction and ipsilateral renal aplasia (The Johns Hopkins Hospital, 1950 to 1980)

Anatomic findings	Patient	Age	Signs and symptoms	Renal agenesis	Uterus	Operation	Subsequent pregnancy
Group 1: Complete unilateral vaginal	B. S.	16	Paravaginal mass, severe dysmenorrhea, lower	Ľeft :	Didelphys	Excision of vaginal septum	Term pregnancy
obstruction with- out uterine	C. C.	21	abdominal pain, regular menses	Right	Didelphys	Excision of vaginal septum	Not desired
communication	M. S.	13		Right	Didelphys	Excision of vaginal septum	Undetermined
•	W. W.	20		Right	Didelphys	Excision of vaginal septum	Infertile
	J. F.	17		Rīght	Didelphys	Excision of vaginal septum	Term pregnancy
	M. L.	21		Right	Didelphys	Excision of vaginal septum	Term pregnancy
Group 2: Incomplete unilateral vaginal	P. M.	17	Lower abdominal pain, severe dysmenorrhea,	Left	Didelphys	Excision of vaginal septum	Not desired
obstruction with-	С. М.	19	excessive foul muco- purulent discharge,	Left	Didelphys	Excision of vaginal septum	Term pregnancy
communication	L. H.	14	intermenstrual bleeding	Right	Didelphys	Excision of vaginal septum	Not desired
	R. P	21		Left	Didelphys	Excision of vaginal septum	Term pregnancy
Group 3: Complete vaginal obstruction with a laterally	<b>A.</b> C.	24	Paravaginal mass, lower abdominal pain, dys- menorrhea, regular	Right	Bicornuate	Hemihysterectomy; excision of vaginal septum	Term pregnancy
communicating double uterus	E. C.	14	menses	Right	Bicornuate	Excision of vaginal septum	Not desired

may be difficult. A generous vaginal pedicle that will retract with healing is essential to prevent vaginal stenosis.

#### Comment

The association of renal agenesis with anomalies of the müllerian ducts has long been recognized. However, the precise relationships during development have remained elusive.

With failure of lateral fusion when there is complete, or almost complete, unilateral müllerian obstruction, ipsilateral renal agenesis is, almost without exception, the rule.

With failure of lateral fusion without obstruction, i.e., a uterus didelphys with a double vagina, there is seldom a kidney anomaly.

On the basis of these clinical observations, it would seem, in these problems of lateral müllerian fusion, that renal agenesis is associated not with failure of a lumen to develop but with failure of the lumen to communicate with the more normally developed side.

However, this relationship is not so exact in the Rokitansky-Kuster-Hauser syndrome. In this syndrome, there is partial müllerian agenesis characterized by bilateral failure of a lumen to develop or communicate, but renal agenesis or other serious kidney malfor-

mations occur in approximately 20% of patients and on one side. This means that 80% of patients with what is apparently an identical müllerian anomaly have normal Lidneys. Thus, as mentioned, the correlation of kidney development with müllerian development seems different in the Rokitansky syndrome as compared with the syndrome of obstructed hemivagina.

It is relevant and probably most significant that in bilateral renal agenesis (Potter's syndrome) Potter<sup>8</sup> reported that in 10 of 13 instances the uterus and vagina were absent or very rudimentary, and in two of the 13 there was a uterus didelphys, but curiously enough, in one of the 13, the uterus and vagina were found to be normal. However, in all instances, the ovary and fallopian tubes were present and of normal size.

Marshall and Beisel<sup>9</sup> noted in the August-Copenhagen rat that the association between renal and ipsilateral müllerian anomalies was very similar to the situation in the human.

Thus, müllerian development and wolffian development are ultimately related or perhaps affected by the same adverse agent but the precise relationship remains unclear.

In all patients with a completely obstructed hemivagina, columnar epithelium was identified histologically on the obstructed side. Bell<sup>10</sup> suggested that the columnar epithelium found cephalad to a point of complete obstruction represented the junction of the epithelium of the descending müllerian tubercle and the upward growing urogenital sinus. Kanagasuntharan and Dassanayakae<sup>11</sup> observed that if the obstruction was incomplete a small communication in the obstructing septum was associated with replacement of the columnar epithelium by squamous epithelium.

Squamous epithelium was found lining the upper vagina in all patients with incomplete obstruction in our series. The original columnar epithelium of müllerian origin may have been replaced by squamous epithelium through the process of metaplasia. This view is supported by the observation that after removal of the septum in patients with complete obstruction, the columnar epithelium found in those patients was slowly replaced by squamous epithelium.

It is interesting that patients with completely obstructed vaginas have vaginal adenosis not related to diethylstilbestrol. This has been emphasized by Hansen and Egholm.<sup>12</sup> It seems reasonable to observe such patients in a manner similar to that for diethylstilbestrolexposed patients.

Twelve patients with a double uterus, obstructed hemivagina, and ipsilateral renal agenesis have been described. In patients with complete obstruction a normal menarche and subsequent regular menses may delay the diagnosis until pronounced dysmenorrhea and lower abdominal pain result from a hematocolpos. In patients with incomplete obstruction, foul-smelling vaginal discharge may be noted. A lateral, ill-defined paravaginal mass of variable size may be present, depending on the size of the vaginal or uterine communication. The demonstration of a laterally communicating double uterus may require hysterosalpingography with catheter studies. A vaginal communication may be demonstrated with careful examination of the vaginal septum with a wire probe.

In this series, the excision of the vaginal septum and evacuation of retained old blood or mucus resulted in complete relief of symptoms. One patient with a laterally communicating uterus underwent hemihysterectomy in addition to excision of the vaginal septum.

Six of seven patients who attempted pregnancy conceived following excision of the vaginal septum. Four patients have not attempted pregnancy. One patient has incomplete follow-up. These observations demonstrate that simple vaginal excision of the septum results in unaltered reproductive performance.

#### REFERENCES

- Woolf, R. B., and Allen, W. M.: Concominant malformations. The frequent simultaneous occurrence of congenital malformations of the reproductive and urinary tracts, Obstet. Gynecol. 2:236, 1953.
- Gilliland, B., and Dyck, F.: Uterus didelphys associated with unilateral imperforate vagina, Obstet. Gynecol. 48:55, 1976.
- 3. Yoder, I. C., and Pfister, R. C.: Unilateral hematocolpos and ipsilateral renal agenesis: Report of two cases and review of the literature, Am. J. Roentgenol. 127:303, 1976
- Nygrenk Persoon, B.: Uterus didelphys with an abortion into a unilateral imperforate vagina, Acta Obstet. Gynecol. Scand. 52:187, 1973.
- Loendersloot, E. W.: Letter to the Editors, Am. J. Obstet. Gynecol. 127:682, 1977.
- 6. Neves-E-Castro, M., Bruges-E-Saavedra, A., Velhena, M. M., and Jones, H. W., Jr.: Lateral communicating double uterus with unilateral vaginal obstruction, Am. J. Obstet. Gynecol. 125:865, 1976.

- 7. Garcia, J., and Jones, H. W., Jr.: The split thickness graft technique for vaginal agenesis, Obstet. Gynecol. 49:328, 1977.
- 8. Potter, E. L.: Bilateral absence of ureters and kidneys, Obstet. Gynecol. 25:3, 1965.
- 9. Marshall, F. F., and Beisel, M. A.: The association of uterine and renal anomalies, Obstet. Gynecol. **51**:559, 1978.
- 10. Bell, B. W.: Further investigations into the chemical composition of menstrual fluid and the secretion of the vagina as estimated from analysis of hematocolpos fluid together with a discussion of the clinical features associated with hematocolpos and a description of the character of the obstructing membranes, Br. J. Obstet. Gynaecol. 21:209, 1912.
- 11. Kanagasuntharan, R., and Dassanayakae, A. G. S.: Nature of the obstructing membrane in primary cryptoamenorrhea, Br. J. Obstet, Gynaecol. 65:487, 1958.
- 12. Hansen, K., and Egholm, M.: Diffuse vaginal adenosis: Three cases combined with imperforate hymen and hematocolpos, Acta Obstet. Gynecol. Scand. 54:287, 1975.

# SO SUCCESSFUL YOU DON'T HAVE TIME TO BE A DOCTOR?

Major Don Anderson recalls his

days in private practice:

"Four days out of my residency, my partner in internal medicine had a heart attack. For four straight years, I was the only one who took night calls in internal medicine. Our rural group practice was servicing a population of around 70,000. Staff meetings alone averaged 12 to 14 hours a month. You get to the point where you're so busy you don't have time to spend with your family, and wish you had more time to spend with the patient.

Time to choose. "Going into the Army left a lot of doors open. Once I spent some time in the Internal Medicine Clinic, and on the ward taking care of patients, and working within an organized system, I started to fall in love again with internal medicine. So the cardiology fellowship I was interested in became kind

of secondary.

Time to do things. "I think practice in the Army has variety. I think the Army offers more free time and less paperwork. There are fewer regulations, fewer things you have to do because of outside forces. And a heck of a lot fewer meetings.

"You know that when you go home at night you're not going to get called in to see an emergency patient. You can spend some time reading and catching up. There's a very structured, organized call system. When you're off, you're off.

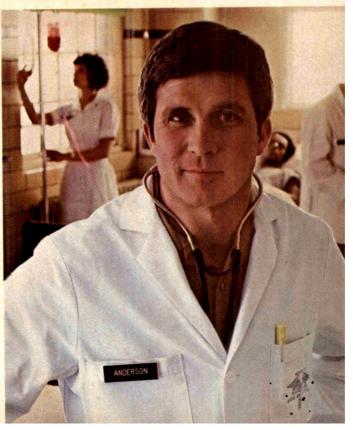
Time to practice. "I think the stereotyped image of the Army Medical Corps doesn't have much basis. It's a relaxed atmosphere. Because of the profession, there are inherent stresses of patient care, but there aren't any additional stresses. You're always a physician. I feel

more a part of a practice here in the Army than I did in civilian life."

If you want a reasonable practice, for a reasonable amount of money, and want to spend a reasonable amount of time with your family, then maybe you should find out more about Army Medicine.
Write: Army Medical Opportunities, P.O. Box 7711, Burbank, CA 91510.

Name	
Address	
City	
State	Zip Co
Homo Phone	Business Pho

Army Medicine.
The practice that's practically all medicine.



# POSITION AVAILABLE:

Board eligible or certified
University trained
Obstetrician, Gynecologist,
to join three man group
in Southern Florida.
Send curriculum vitae to:
Charles Kalstone, M.D.
S. Allen Bradford, M.D.
and Michael P. Born, M.D.
2121 Ponce De Leon Blvd.
Suite 350
Coral Gables, Florida 33134.

## FELLOWSHIP — PRENATAL GENETICS

The Department of Obstetrics and Gynaecology and the Division of Medical Genetics, UCLA School of Medicine, announces the availability of a Genetic Prenatal Diagnosis Fellowship. Applicants should be Board eligible in obstetrics and gynaecology, pediatrics, or family practice. The Fellowship includes didactic training in genetics with emphasis in the clinical application of prenatal diagnosis, didactic training in ultrasound techniques and cytogenetic and biochemical analysis and cellular morphology of amnionic fluid cells. Candidates should apply to:

Dr. Thomas B. Lebherz
Director of OB/GYN Clinics,
Department of Obstetrics and Gynaecology
U.C.L.A. School of Medicine
10833 LeConte Avenue
Los Angeles, California 90024

U.C.L.A. is an Equal Opportunity/Affirmative
Action Employer.

Applications from minority candidates and women are encouraged.

# CLINICAL BIOSTATISTICS:

# here's why you'll benefit from this book

- authoritative articles from <u>Clinical Pharmacology and</u> <u>Therapeutics</u>
- clear and easy-to-read explanations of essential statistical concepts
- provocative insights into the common sense and science behind statistical data

#### **CLINICAL BIOSTATISTICS**

This unique book critically examines the entire field of clinical biostatistics. It presents a series of original articles that first appeared over a five year period in *Clinical Pharmacology and Therapeutics*. Widespread reader acclaim and the timeliness of the subject prompted publication of the essays into convenient book form.

The essays are logically arranged into 29 chapters and organized into five major sections, each preceded by brief commentary written especially for the book. You'll find informative discussions on the diverse statistical techniques used in medical practice and research; research and design problems; presentation of data; and methods of data analysis. Dr. Feinstein has reorganized his original articles to provide you with a completely current guide to the biostatistics used in both clinical and investigative situations. He also offers valuable insights into topics either totally neglected or inadequately covered in conventional texts. Throughout, discussions are written in lively prose style, which makes the subject both interesting to read and easy-to-understand. Why not benefit from Dr. Feinstein's expert guidance firsthand—order your copy of CLINICAL BIOSTATISTICS today!

By Alvan R. Feinstein, M.D., 1977, 468 pages plus FM I-XIV, 6-7/8" x 10", 10 illustrations. Price, \$21.50

#### **ORDER BY PHONE!**

Call toll free (800) 325-4177 ext. 10. In Missouri call collect—(314) 872-8370 ext. 10 during normal business hours.

A80794 Price effective in U.S.A. only.



TIMES MIRROR

THE C V MOSBY COMPANY

11830 WESTLINE INDUSTRIAL DRIVE
ST LOUIS MISSOURI 63141

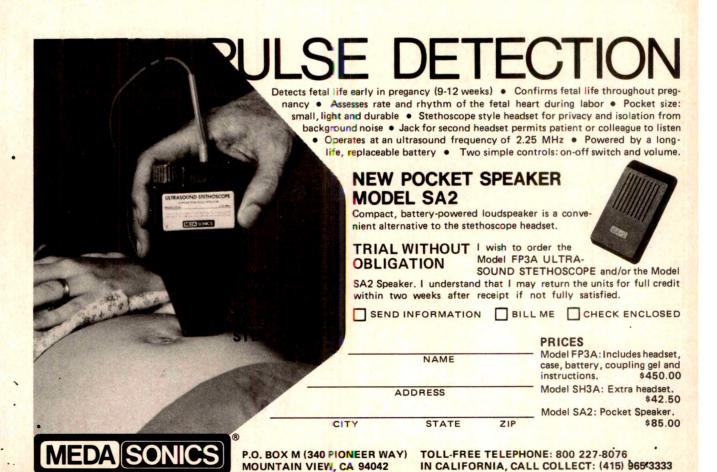
#### **Faculty Position**

The Department of Obstetrics and Gynecology at the University of Utah Medical Center announces the availability of a position in Family Planning at the Instructor or Assistant Professor or Associate Professor level on its full time faculty. Qualifications include Board certification or eligibility and demonstrated ability and interest in teaching, research and patient care. If interested, please send curriculum vitae and bibliography to:

James R. Scott, M.D.
Professor and Chairman
Department of Obstetrics
and Gynecology
University of Utah Medical Center
Salt Lake City, Utah 84132

(Affirmative action/Equal Opportunity Employer) Please respond by: Nov. 30, 1980





## OB/GYN

Prepaid medical group practice, established 1976. Two suburban care centers, each with 3 or 4 BC/BE OBG's. New comprehensive facilities. Well-staffed for clinical support, including Nurse Practitioners and hospital residents. Attractive salary structure and liberal fringes. Starting salary based on experience. Recruitment and relocation expenses covered. Unusually livable city. Send CV or call: Michael R. Soper, M.D. **Medical Director** 6801 E. 117th Street Kansas City, Missouri 64134.

#### **OB-GYN**

OB-GYN to practice in rural multi-specialty group converting to Health Maintenance Organization Excellent opportunity Salary negotiable benefits.

Send resume to Dr. Sam P. Tirimacco Centerville Medical Group RD #1

Fredericktown, Pa. 15333.

#### OBSTETRICIAN-GYNECOLOGIST

OBSTETRICIAN-GYNECOLOGIST—needed in historic Marshall, Michigan, located half-way between Ann Arbor and Kalamazoo, Michigan. Beautiful town with a 77 bed acute care hospital. City population of 7,500 and service area population of 22,000. Admitting staff includes: four (4) Family Practice Specialists, five (5) General Practitioners, two (2) General Surgeons and one (1) Internist. Willing to negotiate to attract a high caliber physician.

#### Contact:

Rob Covert, Administrator, or Philip Glotfelty, M.D., Chief of Staff Oaklawn Hospital 200 North Madison Marshall, Michigan, 49068. Or phone 616-781-4271, extension 201

#### MATERNAL/FETAL MEDICINE

Full time faculty position available. Rank of Assistant or Associate Professor. Busy tertiary referral center offers excellent opportunity for research and teaching within medical school environment. Excellent laboratory facilities available for basic and clinical support. Board eligibility or certification in subspecialty as well as special interest and experience in ultrasonography desirable. Anticipated starting date—position available after January 1, 1981. Recruiting deadline November 30, 1980.

Affirmative Action/Equal Opportunity Employer Competitive Salary and Fringe Benefits Reply with curriculum vitae to:

Charles S. Mahan, M.D.
Chairman, Search Committee
Department of Obstetrics and Gynecology
University of Florida College of Medicine
J. Hillis Miller Health Center
P.O. Box J-294
Gainesville, Florida 32610

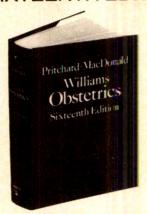
# "...this text is already regarded as scripture."

from a review of the 15th edition in Johns Hopkins Medical Journal, 3/77

ANNOUNCING THE NEW EDITION OF

# Williams Obstetrics

SIXTEENTH EDITION



by Jack A. Pritchard, M.D., Gillette Professor, Department of Obstetrics and Gynecology, University of Texas Southwestern Medical School, University of Texas Health Science Center at Dallas, and Director of Obstetrics, Parkland Memorial Hospital, Dallas and Paul C. MacDonald, M.D., Professor, Department of Obstetrics and Gynecology and Biochemistry, University of Texas Southwestern Medical School, and Director of the Cecil H. and Ida Green Center for Reproductive Biology Sciences, University of Texas Health Science Center at Dallas

This new edition of a classic work reflects the most recent advances in obstetrical care. Its well-balanced presentation of established principles

and new, often controversial, concepts offer you a valuable clinical tool as well as an important reference for your professional library.

Completely updated and revised, WILLIAMS OBSTETRICS, 16th Edition includes over 100 new diagrams and line drawings along with detailed information on the major advances in methodology and technics which have occurred since the last edition. Drs. Pritchard and MacDonald have made the most extensive revisions in the book's coverage of sonography, which is stressed throughout this edition. Thirty-five actual sonograms are included to demonstrate a variety of obstetric conditions. Other areas which have undergone significant revision include estimation of fetal growth and maturity, management of pre-eclampsia/eclampsia, physiology of labor, and indications for fetal monitoring. The authors state in the preface that "it is the most exciting times to be an obstetrician." Their enthusiasm in exploring new tools, such as fetal diagnosis and therapy, make this edition a unique and comprehensive examination of diverse approaches to the practice of obstetrics.

1980 1,224 pp., including 7 full color plates AS

A9731-9

\$48.50



#### **APPLETON-CENTURY-CROFTS**

Medical / Nursing Publishers • Dept. OB/GYN 780 • 292 Madison Avenue, NY, NY 10017

A	-C
	1 0

NAME

Please send	d me on 30-day ap	proval		copy(ies)	1
of WILLIAM	IS OBSTETRICS	, 16th	Edition,	A9731-9,	Ĺ
48.50.					-

I wish to charge my purchase through:

☐ Master Charge ☐ Visa

☐ Master Charge ☐ Vis

Account No. \_\_\_ Expiration Date

Signature

ADDRESS\_\_\_\_\_\_STATE\_\_ZIP

AC0055-7

#### CAREER OPPORTUNITY OBSTETRICS— GYNECOLOGY

Unique opportunity exists for Board Certified/Eligible Obstetrician-Gynecologist seeking a full time position in a multi-specialty group practice.

In addition to an active practice the position offers opportunity for teaching in a residency training program, clinical research, and participation in an active adolescent maternity program.

Excellent incentive compensation system with guaranteed base salary and fringe benefits. Begin summer 1981 or sooner.

Send vitae in confidence to:

William F. Grace, M.D., F.A.C.O.G. Director, Ob/Gyn Division **GENESEE HEALTH SERVICE** MEDICAL GROUP

220 Alexander Street Suite 708 Rochester, New York 14607 (716) 263-5214

An Equal Opportunity Employer, M/F.



COLUMBIA UNIVERSITY **COLLEGE OF PHYSICIANS** & SURGEONS

and ST. LUKE'S - ROOSEVELT HOSPITAL CENTER

in association with the International Society for the Study of Vulvar Disease will present the second postgraduate course for clinicians on

CUTANEOUS-VULVAR AND VAGINAL DISEASES May 14, 15, 16, 1981 New York Academy of Medicine

New York City

Under the Direction of HAROLD M.M. TOVELL, M.D. (Gynecology) ALEX W. YOUNG, M.D. (Dermatology)

For the practicing dermatologist, gynecologist, and family practitioner. An interdisciplinary faculty composed of gynecologists, dermatologists, and pathologists will discuss the diagnosis and management of the common dermatoses, bacterial, parasitic and viral infections which affect the vulva. Sexually transmitted diseases will also be discussed. An indepth review of vulvar dystrophies, premalignant, and malignant conditions will be presented. Pertinent diagnostic methods and specific therapeutic regimens will be emphasized.

Fee: \$375; residents: \$175 (with a letter from departmental chairman); includes lunches, course syllabus and sildes of selected diseases. Approved for 18 credit hours in Category 1 of the A.M.A.'s Physician's Recognition Award, 18 cognates for A.C.O.G. Fellows and 18 prescribed credit hours by A.A.F.P. For application and information contact Dr. Elizabeth C. Gerst, Continuing Education Center, College of Physicians and Surgeons of Columbia University, 630 West 168th Street, New York, New York 10032; telephone (212) 694-3682.

# Choose a practice you can live with.

Hospital Corporation of America knows of many practice opportunities in communities across the nation where we can match a physician's professional needs and personal desires with an attractive community that needs his or her skill.

HCA owns and manages more than 150 hospitals from coast to coast in settings ranging from small, rural towns to large metropolitan centers. Practice opportunities are available in solo, groups, associations, and partnerships.

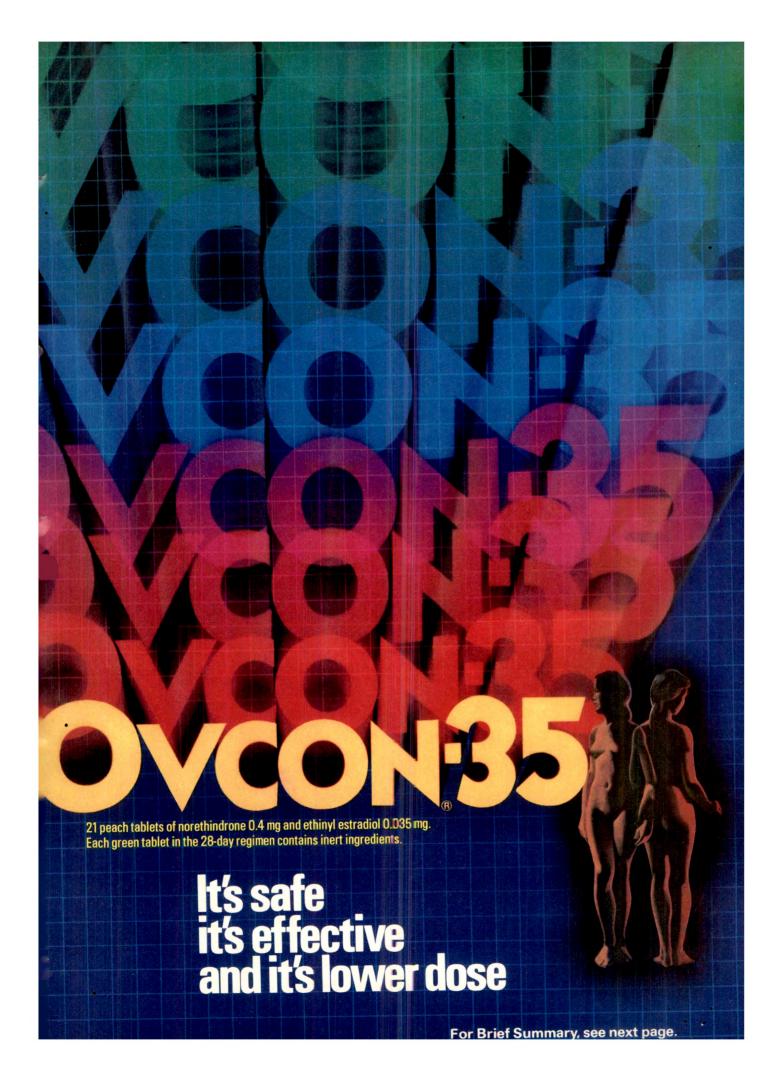
And HCA will help ease the way when you and your practice relocate. Upon

arrival, you should find a solid practice, conveniently located offices, and the medical support and modern equipment you need.

Contact HCA today. Let our free, no obligation Professional Relations Program match your needs with an HCA practice opportunity. Just send your curriculum vitae, along with information on your personal, professional, and geographical interests to:

Charles M. Wooden, Director, Professional Relations, Hospital Corporation of America, One Park Plaza, Nashville, TN 37203. Telephone toll free 1-800-251-2561 or call collect (615) 327-9551.

Hospital Corporation of America.



#### OVCON-35

21 seach tablets of norethindrone 0.4 mg and ethinyl estradiol 0.035 mg. Each green tablet in the 28-day regimen contains inert ingredients.

Indications and Usage: Ovcon is indicated for the prevention of pregnancy. Some combination products containing 35 mcg. or less of ethinyl estradiol report slightly higher pregnancy rates than are reported for the higher dose combination products.

Contraindications: Oral contraceptives should not be used in women with any of the following conditions: 1) Thrombophlebitis or thromboembolic disorders. 2) A past history of deep vein thrombophlebitis or thromboembolic disorders. 3) Cerebral vascular or coronary artery disease. 4) Known or suspected estrogen dependent neoplasia. 6) Undiagnosed abnormal genital bleeding. 7) Known or suspected pregnancy.

Warnings:

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. Women who use oral contraceptives should be strongly advised not to smoke. Use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

contraceptive use. Women who use oral contraceptives should be strongly advised not not contraceptive is associated with increased risk of several serious conditions, including thromboembolism, stocke, myocardial infarction, hepatic adenoma, galibiadder to contraceptive in the contraceptive is well established. Three principal and thrombotic disease associated with use of oral contraceptives is well established. Three principal contraceptive is used to the contraceptive is the contraceptive is well established. Three principal contraces are contraceptive in the contraceptive is the contraceptive in the contraceptive in the contraceptive are 4 to 11 times more likely than nombotic. These studies discusses without evident cause. In a study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhapic stroke was 2.0 times greater than infarction associated with the proater the number of underlying risk factors is conducted in the underlying causes. If was estimated that the risk of hemorrhapic stroke was 2.0 times greater than infarction associated with the upsteen stroke of the contraceptive users and contraceptive users and the contraceptive users who do not smoke (smoking considered amajor predisposing condition to myour contraceptive users who do not smoke have about a 5-fold increased risk of fatal infarction compared to sworth and the contraceptive users and other than the contraceptive users and contraceptive users who do not smoke the contraceptive users and contraceptive users and

oral contraceptive therapy. Embryos with these anomalies are virtually always spontaneously aborted. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping oral contraceptives is unknown. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period and further use of oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is continued to the patient should be apprised of the potential risks to the fetus and the advisability of pregnancy continuation should be discussed in light of these risks. It is also recommended that women who discontinue oral contraceptives with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend three months. Administration of progestin-only or progestin-estrogen combinations to induce withdrawal bleeding should not be used as a test for pregnancy. 6) Gall Bladder Disease. Studies have reported an increased risk of surgically confirmed gallbladder disease appearing after one year of oral contraceptive use and doubling of the risk after 4 or 5 years of use. 7) Carbohydrate and Lipid Metabolic Effects. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. For this reason, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives. In prevalence of triglycerides and total phospholipids have been observed in oral contraceptive users may be no higher than nonusers in the first year of a contraceptive users may be no higher than nonusers in the first year of and contraceptive users may be no higher than nonusers in the first year of oral contraceptive users may be no higher than in o

contraceptives. 12) BreastFeeding. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions: 1) A complete medical and family history should be taken prior to the initiation of oral contraceptives. Examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than 1 year without another physical examination being performed. 2) Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size. 3) Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. 4) Because oral contraceptives may cause some degree of fluid retention, conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, cardiacor renal insufficiency or asthma require careful observation. 5) Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving oral contraceptive therapy. If jaundice while receiving such drugs, the medication should be discontinued. 6) Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7) Oral contraceptive users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. The clinical significance of this is yet to be determined. 8) Serum folate levels may be depressed by oral contraceptive therapy. This may complicate subsequent pregnancy with regard to folate deficiency.

9) The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted. 10) Certain endocrine and liver function tests a

concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient: Detailed Patient Labeling has been prepared for use by the patient and has been made available for distribution by the pharmacist.

Drug Interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbulazone, phenytoin sodium and ampicillin.

Adverse Reactions: An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see Warnings): Thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral thormbosis, cerebral thrombosis, cerebral thrombosis, cerebral thrombosis, or patients of discounting discounting discounting and the use of oral contraceptives, although additional confirmatory studies are needed. Mesenteric thrombosis, benign hepatomas, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10% or less of patients during the first cycle (Other reactions, as a general rule, are seen much less frequently or only occasionally); gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting; change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist, breast changes (tenderness, enlargement, and secretion); change in weight (increase or decrease); change in cervical erosion and cervical secretion possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; r

hemorrhagic eruption, vaginitis, porphyria, impaired renal function.

Acute Overdosage: Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.



©1979 MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA 47721 USA MJL 9-4490

#### COMMUNICATIONS IN BRIEF

This section is suitable for reporting results of therapeutic trials, descriptions of new procedures or instruments, and case reports which illustrate a principle. Reports should be limited to seven hundred words and two references. Use of an illustration or table requires a proportionate reduction in total words.

# Streptococcus sanguis sepsis and meningitis: A complication of vacuum extraction

RICHARD E. HEATH, JR., M.D.
JACK A. ROGERS, JR., M.D.
LAWRENCE V. CHELDELIN, M.D.
ALLEN P. KILLAM, M.D.

Departments of Pediatrics and Obstetrics and Gynecology, William Beaumont Army Medical Center, El Paso, Texas

NEONATAL SEPSIS and meningitis are recognized complications of intrapartum events and obstetric manipulations. The pathogenic microorganism is usually a member of the vaginal flora.

The following case report documents two phenomena not previously reported: the occurrence of sepsis and meningitis as an apparent complication of vacuum extractor application during delivery and the ability of *Streptococcus sanguis* to produce serious neonatal disease.

Patient J. W., a 3,230 gram male infant, was born at term to a 25-year-old, gravida 2, Caucasian mother after an uneventful pregnancy. Clear amniotic fluid was noted upon spontaneous rupture of the membranes 14 hours prior to delivery. Internal monitoring revealed no abnormalities in uterine contractions or fetal heart rate. The delivery was difficult and required vacuum extractor and low outlet forceps assistance. Apgar scores were 8 at 1 minute and 9 at 5 minutes. At birth the physical examination was unremarkable except for mould-

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Reprint requests: Dr. Richard E. Heath, Jr., P. O. Box 70367, William Beaumont Army Medical Center, El Paso, Texas 79920.

ing of the skull, a caput succedaneum, and, at the site of vacuum extractor application, ecchymosis with fine abrasions in one area of its margin. The site of the fetal electrode attachment was noted to be in the parietal area lateral to the ecchymotic area.

At 20 hours of age the infant was noted to be lethargic and feeding poorly. A physical examination revealed a rectal temperature of 100.8° F, irritability, a poor suck reflex, and a high-pitched cry. While the site of the fetal electrode attachment was unremarkable, pustules were found where the abrasions had been observed at birth; stroking of the skin produced an erythematous streak surrounded by areas of pallor (tache cérébrale). The remainder of the physical examination was normal.

Laboratory data included a white blood cell count of 3,200 cells/cu mm with 28 polymorphonuclear cells, 46 band neutrophils, 21 lymphocytes, and 5 monocytes. The platelet count was 179,000/cu mm. Cerebrospinal fluid examination revealed 65 polymorphonuclear cells, 43 lymphocytes, and a protein level of 271 mg/dl. Gram stain of the scalp pustules, cerebrospinal fluid, buffy coat of the blood, and urine revealed gram-positive cocci, subsequently identified by the Center for Disease Control as *Streptococcus sanguis*, Biotype II.

Initial therapy consisted of intravenous ampicillin and gentamicin until the sensitivity of the organism was determined; then aqueous penicillin G was used exclusively. After 24 hours of therapy, the cerebrospinal fluid cultures were sterile, and antibiotic therapy was continued for a total of 28 days. At 3 months of age the infant was thriving and developing normally; he was subsequently lost to follow-up.

Obstetric manipulations are known to increase the risk of neonatal sepsis and meningitis, themselves recognized complications of intrapartum events. While complications of vacuum extraction have been reported, as a search of the literature revealed no mention of serious neonatal infection as a complication of such extraction.

It has been previously documented that organisms can gain access to the host through scalp defects. The rapid appearance of pustules at the site of scalp abrasions, the subsequent development of sepsis and meningitis, and the isolation of the same organism from all culture sources strongly suggest that the organism was acquired in the birth canal through the scalp defect rather than transplacentally.

Many groups of streptococci have been reported to cause serious infections in the newborn infant; however, *Streptococcus sanguis*, while known to cause both endocarditis and meningitis in adults, has not been previously reported as a neonatal pathogen. Commonly found in dental plaque, it is not a routine member of vaginal flora.<sup>2</sup>

Because a newborn infant has compromised host defense mechanisms, he is vulnerable to many infectious agents.<sup>2</sup> Thus, any procedure which disrupts the integrity of the skin should be utilized only after weighing the benefits against the potential risks. If such a procedure is elected, the infant must be carefully evaluated for subsequent signs of serious infection.

We appreciate Dr. Lawrence J. Johnson's review of the manuscript.

#### REFERENCES

- Fanaroff, A., and Klaus, M.: Neonatal infections, in Klaus, M., and Fanaroff, A., editors: Care of the High Risk Neonate, Philadelphia, 1973, W. B. Saunders Company, p. 208.
- Klein, J. O., Remington, J. S., and Marcy, S. M.: An introduction to infections of the fetus and newborn, in Remington, J. S. and Klein, J. O., editors: Infectious Disease of the Fetus and Newborn Infant, Philadelphia, 1976, W. B. Saunders Company, p. 1.
- 3. Malmstrom, T.: The vacuum-extractor: Indications and results, Acta Obstet. Gynecol. Scand. (Suppl. 1) 43:23, 1964.

## Sources of error in the estimation of fetal gestational age

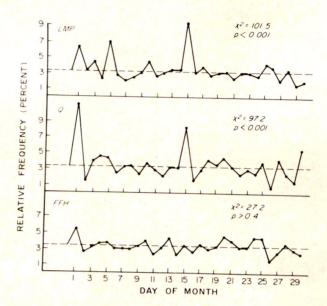
IVAN E. ZADOR, PH.D.
ROGER H. HERTZ, M.D.
ROBERT J. SOKOL, M.D.
VICTOR J. HIRSCH, B.S.

Department of Obstetrics and Gynecology and the Perinatal Clinical Research Center, Cleveland Metropolitan General Hospital/Case Western Reserve University, Cleveland, Ohio

RELIABLE ESTIMATION of fetal gestational age remains an important problem in providing appropriate obstetrical care since errors in its estimation may result in significant morbidity and mortality. Commonly used

Supported in part by United States Public Health Service Grants Numbers 5M01-RR00210 and 1P50 HD11089.

Reprint requests: Ivan E. Zador, Ph.D., Department of Obstetrics and Gynecology, Cleveland Metropolitan General Hospital, 3395 Scranton Road, Cleveland, Ohio 44109.



**Fig. 1.** Distributions of the day of the month on which LMP, Q and first audible unamplified FFH were recorded. The expected frequency of 3.3% per day is indicated by the dotted lines. The distributions of LMP and Q are significantly nonuniform, while that of FFH is uniform, based on goodness-of-fit  $\chi^2$  analysis (27 degrees of freedom).

clinical estimators of fetal gestational age include the date of the patient's last menstrual period (LMP), quickening (Q), and the date the fetal heart tones (FFH) can first be documented by unamplified auscultation. The most commonly used laboratory estimator of fetal gestational age is based on sonographic measurement of the fetal biparietal diameter (BPD). Hertz and associates1 reported that none of these estimators is 100% reliable; the correlation coefficient (r value) of each estimator with the actual gestational age, based on pediatric examination, is less than 0.9. Ideal correlation between two variables is 1.0 (100%). An r value of 0.9 indicates that about 80% of the variance can be explained by the duration of gestation and that the remaining 20% is related to other factors. While some of this variance is undoubtedly related to biologic variation, potentially avoidable factors may be making important contributions. Our purpose in this study was to identify avoidable sources of error in estimating fetal gestational age. Our hypothesis was that, in a large unselected population, the dates of the LMP, Q, and FFH, as well as estimates based upon the BPD measurement, should be uniformly distributed. Failure to demonstrate a uniform distribution of these data would identify potentially correctable sources of error in estimating fetal gestational age.

The study population consisted of 899 consecutive gravid patients examined in the Antenatal Unit at Cleveland Metropolitan General Hospital during a 13-month period. With the use of only results from the last ultrasound examination (to assure statistical inde-

pendence), the LMP, Q, FFH, and BPD data were obtained from the computerized medical record<sup>2</sup> of each patient. BPD data were expressed both in millimeters and in "estimated" weeks' gestation. The statistical hypothesis of uniform distribution was tested by means of  $\chi^2$  goodness-of-fit analysis.

The distributions of LMP, Q, and FFH by day of the month are shown in Fig. 1. Assuming uniform distribution, on the average, 3.3% of each event should occur on each day of the month. LMP dates were found to be nonuniformly distributed throughout the month. Days 1, 5, and 15 were major contributors to the nonuniform distribution with 9% of all LMPs (almost three times the expected value) recorded on day 15. The date of Q was also nonuniformly distributed. As with the LMP, days 1 and 15 exhibited the largest deviations from the expected value, with 10.5% of all Qs recorded on day 1 (more than three times the expected value). On the other hand, the date the fetal heart tones could be documented by unamplified auscultation was found to be uniformly distributed.

Based on our BPD nomograms, it was expected that approximately 18% of the BPD estimates of gestational age would be reported as a "whole week" of gestation (e.g.,  $32^{-9/7}$  weeks,  $33^{-9/7}$  weeks), while 82% would be expected to be reported as "fractional weeks" of gestation (e.g.  $32^{-3/7}$  weeks). Distinct bias was identified in that 32% of the BPD–gestational age estimates were reported as "whole weeks" of gestation, while only 68% of the estimates were reported as "fractional weeks" of gestation ( $\chi^2 = 29.24$ , p < 0.001, degree of freedom = 1).

The key finding of this study is that there is a significant bias in three of the commonly used estimators of fetal gestational age (BPD, LMP, and Q) and that this bias may lead to errors in reliably estimating gestational age. The source of bias in the LMP and Q data is most likely related to the way in which patients report this information (e.g., "My period started in the middle of the month") and then to the way in which the physician records this historical information (e.g., LMP = February 15, 1980). Potential errors stemming from vague LMP data could be minimized by requesting that all gynecologic patients keep menstrual calendars and that they bring them to the physician's office at each visit. As previously suggested, obstetric patients should be requested to record, in writing, the dates of the first three days that they feel fetal movement (Q). The FFH data were probably unbiased, because this parameter reflects the date on which the patient happened to be seen by her physician.

Bias identified in estimating gestational age based on BPD measurements is probably related to the technicians' unconscious preference for finding a BPD measurement that corresponds to a "whole number" of weeks (e.g., 32 % rather than 32 % weeks).

The results of this study suggest that greater attention to details should improve clinical care by eliminat-

ing potentially avoidable sources of error in estimating. fetal gestational age.

#### REFERENCES

 Hertz, R. H., Sokol, R. J., Knoke, J., Rosen, M. G., Chik, L., and Hirsch, V.: Clinical estimation of gestational age: Rules for avoiding preterm delivery, Am. J. Obstet. Gynecol. 131:395, 1978.

2. Sokol, F. J., Rosen, M. G., Stojkov, J., and Chik, L.: Clinical application of high risk scoring on an obstetric service, Am.

J. OBSTET. GYNECOL. 128:652, 1977.

Estimation of success in treatment of premature labor: Applicability of prolongation index in a double-blind, controlled, randomized trial

L. L. PENNEY, M.D. W. C. DANIELL, M.D.

Department of Obstetrics and Gynecology and Clinical Investigations Service, William Beaumont Army Medical Center, El Paso, Texas

Variability in gestational age at entry, diagnosis of premature labor, length of extension of pregnancy, and eventual fetal outcome causes difficulty in evaluating the success of any therapy for premature labor. In an effort to identify a satisfactory parameter with which to correlate results the tocolysis index (TI)<sup>1</sup> and the prolongation index (PI)<sup>2</sup> have been introduced. We have examined the usefulness of the latter in a double-blind, randomized study of terbutaline administered for premature labor.

The protocol was approved by the hospital Human Use Committee and each patient gave informed consent. The length of gestation was more than 24 but less than 36 weeks at initiation of treatment. Uterine contractions were regular as recorded by external monitor in all patients and cervical dilatation was 4 cm or less. Patients with ruptured membranes, abruptio placentae, or cervical cerclage were not studied. Thirty-three patients participated, and 18 of these received placebo.

The treatment schedule was  $10~\mu g/minute$  intravenously until contractions ceased, then 0.25~mg subcutaneously every 2 to 4 hours, and eventually 2.5~mg orally every 2 to 4 hours for maintenance. The trial continued for 18~months until stopped by a Food and Drug Administration directive in July, 1979.

Comparison of the TI and neonatal outcome, respectively, to the PI by the Spearman rank correlation

Reprint requests: Dr. L. L. Penney, Department of Obstetrics and Gynecology, William Beaumont Army Medical Center, El Paso, Texas 79920.

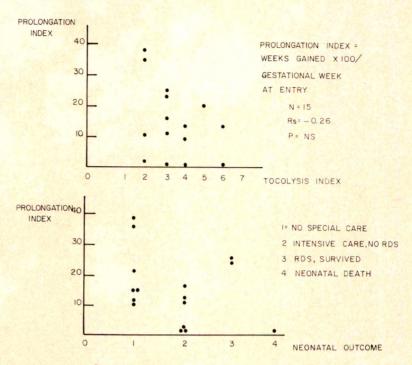


Fig. 1. Correlation of PI with the TI and neonatal outcome.

coefficient,3 as suggested by Richter,2 revealed no statistically significant correlation in either case. The data are displayed in Fig. 1. Individual cases are illustrative. Whereas Richter found 4/125 patients with a TI of 6, we found 2/15. The PI in all four of Richter's patients was less than 5. While one of our patients did have a PI of 1, the other had a PI of 14. Furthermore, Richter<sup>2</sup> states "at a TI of 6 the treatment was absolutely incompetent." Our two patients with a TI of 6 were delivered at 34 weeks' gestation after 3 days of treatment and at 371/2 weeks' gestation after 33 days of treatment. Neither infant had any difficulty. PIs less than 8 were said to "indicate failure of treatment."2 Four of 15 patients in this treated study group had PIs less than 8; however, three of the four infants did well and did not develop respiratory distress syndrome (RDS). The fourth did develop RDS and died. Two additional infants developed RDS. Paradoxically the PIs of 25 and 23 in these two cases ranked third and fourth highest of the entire group. The incidence of 2/2 contrasts to 2/12 of Richter's patients with RDS and PIs more than 20, but 10/2 with RDS and PIs less than 10.

We conclude the PI did not correlate well with the TI or with neonatal outcome in a double-blind trial of terbutaline for premature labor. Although it appears to be a more sophisticated and logical approach to judging the effective length of therapy, the PI is most insensitive to the critical factor of neonatal outcome.

#### REFERENCES

 Baumgarten, K., and Gruber, W.: Tokolyseindex, in Dudenhausen, J. W., and Saling, E., editors: Perinatale Medizin, Stuttgart, 1974, vol. 5, Georg Thieme Verlag.

- Richter, R.: Evaluation of success in treatment of threatening premature labor by betamimetic drugs, Am. J. Obstet. Gynecol. 127:482, 1977.
- 3. Snedecor, G. W., and Cochran, W. G.: Statistical Methods, ed. 6, Ames, Iowa, 1967, Iowa State University Press, p. 192.

## Hematocolpometra in the presence of normal menstruation

TERRANCE S. DRAKE, COMMANDER, MC, USN, F.A.C.O.G.

WILLIAM F. O'BRIEN, LIEUTENANT COMMANDER, MC, USNR

Department of Obstetrics and Gynecology, National Naval Medical Center, Bethesda, Maryland

HEMATOCOLPOMETRA is an infrequent but important condition caused by obstruction to menstrual flow. As imperforate hymen is the most frequent etiology, the patient classically presents with primary amenorrhea, cyclic lower abdominal pain, and a pelvic mass. We report on two young women in whom hematocolpometra was accompanied by normal menses. In both

The opinions and assertions contained herein are those of the author and not to be construed as official or as reflecting the views of the Navy Department or the naval service at large.

Reprint requests: Terrance S. Drake, M.D., Reproductive Endocrinology Section, Department of Obstetrics and Gynecology, National Naval Medical Center, Bethesda, Maryland 20014. patients a uterus didelphys was associated with a complete transverse vaginal septum with unilateral obstruction to menstrual flow. Correct preoperative diagnosis relies upon an understanding of the anomalies which may occur in the female reproductive tract and a high degree of clinical suspicion.

In Case 1, a 13-year-old white girl experienced menarche 6 months prior to evaluation. She had developed severe dysmenorrhea during the two cycles preceding initial presentation. Evaluation at another institution revealed an 8 cm pelvic mass, and hysterosalpingography revealed a left uterus unicornis. An intravenous pyelogram was normal. At laparoscopy, a left unicornuate uterus with a right "functioning" rudimentary horn was described.

The patient was transferred to this institution for removal of the right uterine horn. At exploratory celiotomy a uterus didelphys with unilateral obstruction was found. The diagnosis of "functioning" rudimentary horn was discarded and no further intra-abdominal procedure was performed.

A transvaginal incision of the transverse septum at the level of the cervix allowed the egress of 200 ml of dark fluid. Following operation the pelvic mass and dysmenorrhea resolved. Eight months following the primary procedure a more complete septal excision was performed.

In Case 2, a 12-year-old, white girl experienced menarche 5 months prior to evaluation. She presented with increasing dysmenorrhea during the preceding three cycles. Physical examination revealed a 6 cm right paravaginal mass contiguous with an 8 cm pelvic mass. An intravenous pyelogram demonstrated absence of the right kidney and collecting system. The patient underwent partial septal excision with resolution of the paravaginal and pelvic masses as well as relief of the dysmenorrhea. Twelve months after the initial procedure a more complete septal excision was performed.

In a review of congenital anomalies of the female genital tract Semmens<sup>1</sup> found an incidence of 1/625 deliveries and 1/1,800 gynecologic patients.<sup>1</sup> Although the true incidence of each type of anomaly is unknown, many categories of fusion defects have been described. The unusual occurrence of normal menstruation in the presence of hematocolpometra was also described by Purslow<sup>2</sup> in 1922.

Although the patients reported here presented with identical symptoms, management varied greatly. In the first patient incorrect diagnosis led to an unnecessary celiotomy. In addition to clinical suspicion, the position of the septum influenced the ability to correctly diagnose the malformation preoperatively. Fig. 1 illustrates the septal position in these two patients. The high position in the first patient contributed to the faulty diagnosis. Because of the lower position of the septum in Case 2 a paravaginal mass was easily appreciated and celiotomy was not done.

Unlike the patient with uterus unicornis with a "functioning" rudimentary horn, abdominal exploration is not necessary in patients with menstrual obstruction caused by a vaginal septum.<sup>3</sup> Since the major therapeutic objective is the establishment of menstrual drainage, treatment should consist of simple transvaginal septal excision. In both patients anatomic distortion

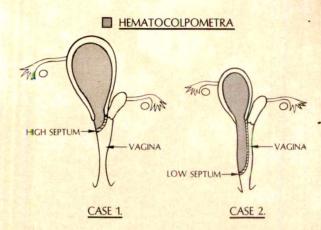


Fig. 1. A comparison of septal position in the two patients.

at the initial operation prevented adequate excision and a more definitive procedure was carried out at a later time.

The relative ease with which surgical management may be accomplished in these patients does not dismiss the need for intravenous pyelography. Absence of a kidney noted in one of our patients underscores the importance of urologic evaluation in all patients believed to have a female reproductive tract anomaly.

#### REFERENCES

- L Semmens, J. P.: Congenital anomalies of the female genital tract. Functional classification based on a review of 56 personal cases and 500 reported cases, Obstet. Gynecol. 19:328, 1962.
- Purslow, C. E.: A case of unilateral haematokolpos, haematometra, and haematosalpinx, Br. J. Obstet. Gynaecol. 29:643, 1922.
- McRae, M. A., and Moon, H. K.: Dysmenorrhea in the uterus unicollis with rudimentary uterine cavity, Obstet. Gynecol. 53:134, 1979.

# Fatal influenzal pneumonia in pregnancy: Failure to demonstrate transplacental transmission of influenza virus

REUBEN RAMPHAL, M.D.
WILLIAM H. DONNELLY, M.D.
PARKER A. SMALL, JR., M.D.

Departments of Medicine, Pathology, and Immunology and Medical Microbiology, University of Florida, College of Medicine, Gainesville, Florida

INFLUENZA INFECTION of pregnant women has been blamed for subsequent fetal abnormalities. Viremia,

Supported by United States Public Health Service Grant AI-07713 and a Fellowship from the Medical Research Council of Canada (R. R.)

Reprint requests: P. A. Small, Jr., M.D., Box J266 JHMHC, University of Florida, Gainesville, Florida 32610.

transplacental transmission of the virus, and subsequent fetal infection have been the proposed mechanisms. Evidence for transplacental transmission is scant, but such transmission has been observed in man and animals. In this case of influenza in a pregnant woman we were unable to document transplacental passage of the virus.

The patient, a 23-year-old white woman, para 0-0-1-0, was known since childhood to have a ventricular septal defect and had undergone a therapeutic abortion 2 years prior because of heart disease. She was admitted to the Shands Teaching Hospital at term pregnancy with a 2-day history of "cold" symptoms—headache, fever, chest pains, and shortness of breath. There was no record of her having received an influenza vaccination during the current pregnancy. She appeared ill and in distress but was acyanotic. The temperature was 40° C. She had wet rales throughout the lung fields, a harsh systolic murmur, and an S<sub>3</sub> gallop rhythm audible over the precordium. The fetal heart rate was 160 bpm. Chest films demonstrated diffuse bilateral interstitial infiltrates and consolidation of the right lower lobe.

The hospital course was one of steady deterioration. She became increasingly hypoxemic and cyanotic despite oxygen therapy. Fetal heart sounds were lost suddenly 48 hours after admission, before a cesarean section could be performed, and the patient died 12 hours later. Blood cultures were growing *Streptococcus pneumoniae* at the time of death. At autopsy the airways were scarlet and the lungs consolidated, gray-red, and firm. Microscopic studies showed that the upper airway mucosa had sloughed and the alveoli had the characteristic changes of viral pneumonia along with colonies of grampositive cocci in the lower lobes. The heart had a large ventricular septal defect. The fetus was covered with dark green meconium but gross and microscopic studies were all normal.

During the autopsy, tissues and blood from both the mother and child were collected for virologic and serologic studies. An influenza A virus (H3N2) was isolated from maternal tracheal mucosa and secretions, lungs, and pulmonary blood. The isolate was subsequently characterized as "A/Texas/77-like." Fetal samples (amnion, placenta, lung, tracheal mucosa, pleural fluid, and blood) did not yield an influenza virus, even on further blind passage in embryonated eggs. Serologic studies of the woman's blood taken at admission and at autopsy lacked detectable antibody titers to this particular influenza virus (<8 hemagglutination inhibition units) and had very low titers (8 hemagglutination inhibition units) to other closely related H3N2 influenza viruses, which had circulated in the population since 1968. The fetal titers were the same as maternal titers.

This case illustrates several points. It shows that transplacental transmission of influenza virus is not a consistent occurrence<sup>2</sup> even in the face of overwhelming disease. Animal studies suggest that the site of maternal infection, i.e., lungs or airways, and the virulence and the tropism of the infecting virus are important determinants of transmission. Second, and even more significant, was the relationship between the lack of serum antibody and the lethal pneumonia. Although the role of serum antibody in preventing the rhinotracheitis of influenza may be in doubt, the role of serum antibody in preventing the lethal pneumonia

caused by this virus is clear. Unfortunately, our patient lacked this protection.

Parenteral vaccination is one sure way of inducing serum antibody in adults. However, the current recommendations for influenza vaccination do not include pregnant women as a high-risk group unless they have a concomitant chronic illness.<sup>3</sup> Although there may have been fewer fatal cases of influenza in pregnancy in recent years, cases such as this cause us to question this recommendation. We argue that since killed influenza vaccines are not a greater threat to mother or fetus than to individuals with chronic illnesses, maternal vaccination may be advisable to prevent the occasional cases of maternal and fetal death due to influenza pneumonia and its sequelae.

We are grateful for the technical assistance of Ms. D. Birdsell. We also appreciate the helpful discussions with Robert Cogliano, Robert Yetter, and Dr. Phil Gordon.

#### REFERENCES

- MacKenzie, J. S., and Houghton, M.: Influenza infections during pregnancy: association with congenital malformations and subsequent neoplasms in children, and potential hazards of live virus vaccines, Bacteriol. Rev. 38:356, 1974.
- Yawn, D. H., Pyette, J. C., Joseph, J. M., Eichler, S. L., and Garcia-Bunuel, R.: Transplacental transfer of influenza virus, JAMA 216:1022, 1971.
- Recommendation of the Public Health Service Advisory Committee on Immunization Practices, Morbid. Mortal. Weekly Rep. 28:231, 1979.

#### Abdominal sacral colpopexy

W. COWAN, M.D., F.R.C.S.(C.)
H. R. MORGAN, M.D., F.R.C.S.(C.),
F.A.C.O.G.

Department of Obstetrics and Gynecology, McMaster University, Hamilton, Ontario, Canada

FEW CONDITIONS that a gynecologist faces are more frustrating than prolapse of the vaginal vault following vaginal or abdominal hysterectomy. Consequently, the variety of procedures developed to cure this problem is limited only by the number of individuals who have concerned themselves with it. The aim of treatment is to eliminate the prolapse and enterocele permanently and to leave a satisfactorily functional and anatomically correct vagina without painful or rigid scarring, regardless of age.

Of those abdominal procedures that have been devised, those that pull the vaginal vault forward from its normal anatomic location may be doomed to a high

Reprint requests: Dr. H. R. Morgan, McMaster Clinic, Henderson General Hospital, Hamilton, Ontario, Canada L8V 1C3. failure rate because of the exaggerated exposure of the posterior vaginal vault to continued intra-abdominal pressure. Therefore, it is considered to be anatomically correct that the vaginal vault should be suspended in the posterior portion of the pelvis by attaching it to the sacrum, which serves to pull it upward and backward in its normal direction.

Such a procedure was described in a very complete fashion by Birnbaum<sup>1</sup> in 1973 and by Feldman and Birnbaum<sup>2</sup> in 1979. This operation has been performed in our hospital with consistently good results in 39 patients.

The operation can also be combined with other reparative procedures that may be necessary. Anterior and posterior vaginal repair can be done easily in conjunction with the vault suspension. The repair is best completed prior to the suspension simply because an operation on the anterior or posterior vaginal wall is rendered extremely difficult after the colpopexy because of the new depth of the suspended vagina.

These patients frequently may have some urinary dysfunction that would respond to a simple retropubic urethropexy.<sup>3</sup> The operation has not been used in conjunction with abdominal hysterectomy in the belief that the possibility of a vault abscess with a chronically infected synthetic fabric sling may well cause insurmountable complications in the nature of a draining sinus.

Two important modifications of the Birnbaum technique have been made. First of all, the patient is placed in a froglike position on the operating table in order that the operator's left hand may enter the vagina at the appropriate moment to facilitate the placing of vaginal vault sutures.3. This eliminates the possibility of perforation of the vagina and the attending complication of an infected synthetic mesh link. Second, we feel that the space below the mesh, between the posterior vaginal wall and the anterior surface of the rectosigmoid, constitutes a potential site of internal hernia. We believe this difficulty has been obviated by the use of either one of two methods: sewing the anterior rectal wall to the posterior vaginal peritoneum with a nonabsorbable suture or second, and perhaps preferably, extending the presacral incision in the peritoneum down through the pouch of Douglas and up the back of the vagina, thus giving the opportunity of completely burying the mesh in a retroperitoneal location.

Thirty-nine patients have been treated in such a fashion. The ages of the patients were evenly distributed around the mean of 54.5 years, with a range of 33 to 78 years of age. All patients had had a previous hysterectomy and many had had other previous pelvic surgical procedures: Twenty-one had had previous vaginal repairs, six had had urethrovesical suspension, one had had a vaginal vault sling of the Ulfelder-Parson's type, and one had had a cystectomy and sigmoid ureterostomy for extrophy of the bladder in childhood.

• The patient is placed on the operating table in the

above-described froglike position. If a retropubic procedure for anatomic stress incontinence is to be carried out, a Foley catheter is placed in the bladder. The abdomen is then opened by either a low midline incision or a transverse incision. The former is perhaps somewhat more advantageous as it gives much easier access to the sacral promontory. The intestines and sigmoid colon are packed off upward and to the left to give easy access to the anterior surface of the sacrum. A vertical incision, extending from just below the sacral promontory down through the pouch of Douglas and up onto the back of the vagina, is carried out. Care should be taken at this stage to incise only the peritoneum to avoid troublesome bleeding and possible interference with the blood supply of the upper rectum. The areolar tissue over the body of the second sacral segment is cleared by sharp and blunt dissection with care to avoid damage to and bleeding from the middle sacral vessels. Occasionally it may be necessary to ligate the vessels with a fine chromic suture. A synthetic fabric mesh material (originally Mersilene, more recently Prolene) is attached to the anterior sacral ligament with two or three solid interrupted bites of nonabsorbable suture. The operator's left hand is then placed in the vagina and the vaginal vault is identified. Two or more sutures of nonabsorbable material are placed through the uterosacral ligaments adjacent to the vault, and the tough perivaginal fascia is also picked up in the midline. Tension is placed on these sutures to approximate the new position of the vaginal vault and the synthetic fabric bridge is cut to the appropriate length. The vaginal sutures are then passed through the lower end of the mesh and tied securely. The operator's hand is removed from the vagina, and the glove changed. The final step is to obtain complete hemostasis and to close the peritoneal edges in front of the now completely retroperitonealized synthetic fabric sling. Following completion of the vaginal vault suspension and closure of the abdominal peritoneum, a retropubic procedure can be carried out if indicated.

There has been one failure with the recurrence of vaginal vault prolapse. At a subsequent operation, the distal end of the mesh was found to have separated from the vaginal vault and was embedded beneath the peritoneum, covering the right uterosacral ligament at a distance of about 4 cm from the vaginal vault.

Complications have included two patients who developed a draining sinus in the vaginal vault with exposure of the fabric. In one case this was resolved by simple excision of the exposed fabric, and in the second case, complete rejection of the entire portion of sling material through the vault resulted in spontaneous healing with continued good support of the vagina.

In those operations not accompanied by a retropubic urethropexy, there has been no subsequent urinary stress incontinence. On specific questioning, there has been no evidence that sexual function in those patients who were sexually active prior to the operation has been disrupted. As a matter of fact, there has been a marked improvement in sexual function in this group. Follow-up has been assiduously carried out in all patients. Fourteen of these have been followed up from 3 to 5 years. Twelve patients have been followed from 1 to 3 years, and the remaining 13 have been followed up for 1 year or less. The average length of follow-up has been 2½ years. During this period of observation one failure, as mentioned above, has been noted. The remaining 38 patients continue to enjoy good vaginal support and are without pelvic complaints.

Complications that are specifically related to the procedure include two patients with draining vault sinuses, as mentioned, two who developed postoperative thrombophlebitis, two who developed postoperative atelectasis, one with superficial infection of the abdominal wound, and one case of prolonged postoperative intestinal ileus.

We believe that this operation, which is relatively simple to perform and attended by a low complication rate and a high degree of success, is at present the treatment of choice for posthysterectomy vaginal vault prolapse.

#### REFERENCES

- 1. Birnbaum, S. J.: Rational therapy for the prolapsed vagina, Am. J. Obstet. Gynecol. 115:411, 1973.
- Feldman, G. B., and Birnbaum, S. J.: Sacral colpopexy for vaginal vault prolapse, Obstet. Gynecol. 53:399, 1979.
- 3. Cowan, W., and Morgan, H. R.: A simplified retropubic urethropexy in the treatment of primary and recurrent urinary stress incontinence in the female, Am. J. Obstet. Gynecol. 133:295, 1979.

# Benign glandular inclusions in para-aortic lymph nodes: A cause for false positive lymphangiography

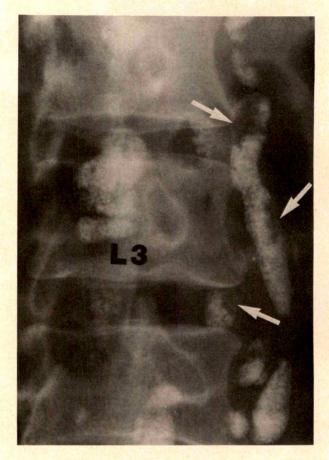
VOLKER SCHNEIDER, M.D. JAMES W. WALSH, M.D. DEAN R. GOPLERUD, M.D.

Departments of Pathology, Radiology, and Obstetrics and Gynecology, Virginia Commonwealth University, Medical College of Virginia, Richmond, Virginia

Benign Glandular inclusions in pelvic lymph nodes are an incidental finding in 14% to 40% of all lymphadenectomies. This entity was found to have no clinical significance in a recent review article in this Journal. We report a patient in whom the presence of benign glandular inclusions in para-aortic lymph nodes caused a false positive preoperative lymphangiogram.

A 43-year-old black woman, gravida 1, para 1, was admitted

Reprint requests: Dr. Volker Schneider, Box 453, Medical College of Virginia, Richmond, Virginia 23298.

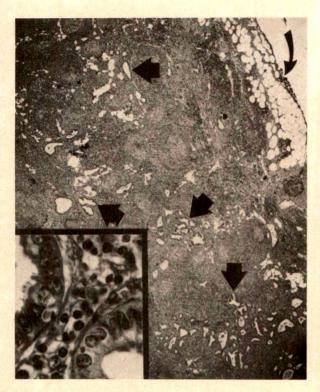


**Fig. 1.** Oblique view of the lumbar spine 24 hours after lymphangiogram shows peripheral defects (arrows) in three left para-arotic lymph nodes consistent with metastases.

for treatment of a keratinizing Stage IIIB squamous cell carcinoma of the cervix. A preoperative lymphangiogram showed peripheral defects in three para-aortic lymph nodes consistent with metastases (Fig. 1). Laparotomy became necessary to treat a right tuboovarian abscess by salpingo-oophorectomy. Bilateral para-aortic and pelvic nodes were sampled by a retroperitoneal lymph node dissection. A postoperative flat plate of the abdomen confirmed removal of abnormal left para-aortic nodes.

The para-aortic lymph nodes contained clusters of gland-like spaces lined by a single layer of cuboidal epithelium (Fig. 2). Cilia were noted on the luminal surface of some of the cells. No endometrial stroma was seen. The inclusions were seen in peripheral as well as central portions of the lymph nodes. Multiple step sections failed to reveal metastatic carcinoma.

The value of lymphangiography for the staging of gynecologic malignancy is controversial. False positive readings represent a significant part of the problem. Histologically, sinus histiocytosis, follicular hyperplasia, fibrosis, hyalinosis, vascular transformation, immunoblastic lymphadenopathy, intranodular fibrolipomatosis, granulomatous disease, and radiation changes have all been described as potential causes for false positive readings of lymphangiograms.<sup>2, 3</sup> Benign



**Fig. 2.** Histologic sections of para-aortic lymph nodes reveal numerous epithelium-lined cystic spaces (*arrowheads*). Lymph node capsule and perinodular fat are seen at the top, right (*curved arrow*). Inset at higher magnification shows a single layer of epithelium with occasional cilia. (hematoxylin and eosin. ×25. Inset ×520.)

glandular inclusions are usually few in number and have not been reported to cause filling defects in lymphangiograms. They have been mainly of concern to the pathologist as a cause for erroneous interpretation as metastatic adenocarcinoma during frozen section examination. In this case, the intranodal glandular inclusions were unusually numerous and caused peripheral filling defects in the lymphangiogram. Since benign glandular inclusions involve mainly para-aortic and pelvic lymph nodes, the gynecologic oncologist should be aware that this entity may interfere with correct interpretation of lymphangiograms.

#### REFERENCES

- Schnurr, R. C., Delgado, G., and Chun, B.: Benign glandular inclusions in para-aortic lymph nodes in women undergoing lymphadenectomies, Am. J. Obstet. Gynecol. 130: 813, 1978.
- Abt, A. B., Murphy, W. L., O'Connell, M. J., and Wierneck, P. H.: False positive lymphography in Hodgkin's disease: A histologic-lymphadenographic correlation, Med. Pediatr. Oncol. 3:253, 1977.
- 3. Clouse, M.E.: Benign lymph node disease, in Clouse, M. E., editor: Golden's Diagnostic Radiology Series, Section 7, Clinical Lymphography. Baltimore, 1977, The Williams &
- Wilkins Co., pp. 122-140.

Human pasteurellosis: The first reported case of *Pasteurella multocida* septicemia and peritonitis during pregnancy

WING K. KAM, M.D., PH.D. HARRY W. HAVERKOS, M.D. HARVEY M. RODMAN, M.D. RALPH SCHMELTZ, M.D. DAVID H. VAN THIEL, M.D.

Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, and Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio

In 1944, Robinson¹ reported the case of a 20-year-old African woman whose blood culture obtained 3 days after spontaneous abortion at 28 to 30 weeks of gestation grew out *Pasteurella multocida*. In 1971, Strand and Helfman² reported a case of chorioamnionitis secondary to *P. multocida* with premature delivery at 32 weeks of gestation followed by death of the infant from possible neonatal sepsis. Interestingly, the same organism was isolated retrospectively from the patient's pet cat.

We report here the first case of *P. multocida* septicemia with peritonitis in a pregnant woman diagnosed before delivery. Of note is the fact that both the mother and infant survived, probably as a result of early recognition and long-term antibiotic treatment.

D. F., a 34-year-old white woman, gravida 1, para 0, was admitted to another hospital at 29 weeks of gestation with severe lower abdominal pain, nausea, vomiting, diarrhea, and fever. Past medical history was noncontributory. On physical examination, temperature was 39° C; blood pressure, 110/60 mm Hg; pulse, 132 bpm; and respiratory rate, 28/min. Moderate abdominal rigidity with rebound tenderness was noted. Fetal heart sounds were heard. The total white blood cell count was 22,100/cu mm with a shift to the left (15% bands). An exploratory laparotomy was performed on the day of admission for the presumed diagnosis of either acute appendicitis or torsion of the ovary. An appendectomy, a myomectomy of two uterine leiomyomas from the anterior uterine wall, and a left salpingo-oophorectomy because of an 8 by 11 cm ovarian cystadenoma were performed. Purulent material from the pelvic gutter on culture grew out P. multocida, sensitive to all antibiotics screened. Examination of the appendix showed hemorrhage into the lumen, lymphoid hyperplasia of the mucosa, and serosal congestion, but no perforation. Postoperatively, the patient was treated with intravenous cephalothin, 500 mg every 6 hours for 1 day, and subsequently with ampicillin, 2 gm every 6 hours intravenously for another 4 days. She was discharged 8 days after admission, afebrile and without medication.

One week after discharge the patient was readmitted with weakness, fever, shaking chills, and right abdominal and flank pain. Physical examination revealed a temperature of 40° C, a

Reprint requests: W. K. Kam, M.D., Ph.D., 1000G Scaife Hall, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261.

pulse of 124 bpm, a respiratory rate of 28/min, and lower abdominal tenderness. Total white blood cell count was 16.200/cu mm, again with a left shift (17% bands). Two blood cultures, obtained on admission, grew out *P. multocida* with antibiotic sensitivities identical to those of the peritoneal culture obtained at the time of her previous admission. She was treated with intravenous ampicillin for 2 days and became afebrile. She was continued on a regimen of oral ampicillin for an additional 6 days and was discharged, again afebrile and without medication.

Three days later, at 33 weeks of gestation, she was admitted to Magee-Women's Hospital with recurrent fever, chills, and abdominal pain. Historical review resulted in the discovery that she had been scratched by her kitten several weeks before her first admission with P. multocida peritonitis. The only remarkable physical finding at this time was slight tenderness in the right upper quadrant. As before, fetal heart sounds were audible at a rate of 160/bpm. Admission white blood cell count was 24, 700/cu mm (15% bands). A fetal activity stress test was normal. Abdominal sonogram revealed no abscess. Two blood cultures were obtained and intravenous treatment was initiated with 30 million U of penicillin G, 240 mg of gentamicin, and 1,200 mg of clindamycin per day in divided doses. Both blood cultures were positive for P. multocida. The API 20 E system\* profile was 0040524. Gentamicin and clindamycin were discontinued and penicillin G was reduced to 10 million U daily on day 9. On day 11 and day 13 repeat blood cultures were negative. She was discharged on day 20 on a regimen of 500 mg of penicillin VK four times a day orally for the remainder of her pregnancy.

Six weeks after discharge the patient was readmitted to Magee-Women's Hospital for induction of labor. She was delivered of a 7 pound, 5 ounce normal baby girl with Apgar scores of 8 at 1 minute and 9 at 5 minutes. The placenta appeared normal on examination. Penicillin was discontinued after delivery. Both mother and infant have remained well. Nose and throat cultures of mother and infant have failed to grow any pathogens.

For several reasons, we suspect that human infections due to P. multocida are probably more common than is generally recognized and suggested by the clinical literature. First, the major source of the infection is either a common household pet bite or a cat scratch, both of which are rather common occurrences. Second, P. multocida is a common bacterium found in healthy cats (estimated 50% to 90%) and dogs (estimated 14% to 54%). Third, superficial wounds from one's own pet usually are not cultured. Fourth, due to its superficial resemblance to Hemophilus, Neisseria, and Mimae, P. multocida may be reported as one of these species and be discarded when cultured because of the low index of suspicion for these organisms. Fifth, the organism is sensitive to most antibiotics used for the clinical treatment of animal bites and, sixth, there is a lack of mandatory requirements for such reporting.

Finally, we suspect, but cannot prove, that the survival of our patient and her child, unlike previously reported cases, was due to the early recognition of the

\*Analytab Products, 200 Express St., Plainview, New York 11803.

infecting organism and the prolonged antibiotic therapy she received.

In addition to toxoplasmosis and cat-scratch disease, human pasteurellosis is another disease mediated by cats and a potential life-threatening one for both mother and fetus.

#### REFERENCES

- Robinson, R.: Human infection with Pasteurella septica, Br. Med. J. 2:725, 1944.
- Strand, Č. L., and Helfman, L.: Pasteurella multocida chorioamnionitis associated with premature delivery and neonatal sepsis and death, Am. J. Clin. Pathol. 55:713, 1971.

# Hysterosalpingography in young infertile patients with unsuspected endometrial adenocarcinoma

JOSEPH MENCZER, M.D. YAIR FRENKEL, M.D. DAVID M. SERR, M.D.

Department of Obstetrics and Gynecology, The Chaim Sheba Medical Center, Tel-Hashomer, and Tel-Aviv University Medical School, Tel-Aviv, Israel

AMONG PATIENTS with endometrial adenocarcinoma only 1% to 8% are under the age of 40, and in those patients a high rate of anovulation and infertility has been reported.

This report describes three young women with prolonged anovulation and primary infertility who underwent hysterosalpingography (HSG) as part of an in-

Reprint requests: Dr. Joseph Menczer, Department of Obstetrics and Gynecology, The Chaim Sheba Medical Center, Tel-Hashomer, Israel.

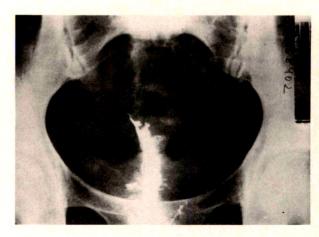


Fig. 1A. HSG (Patient Ch.S.) showing filling defects and intravasation of contrast material.



Fig. 1B. Curettings of same patient in Fig. 1A showing well-differentiated endometrial adenocarcinoma. (Hematoxylin and eosin. ×200.)

fertility workup; HSG demonstrated filling defects which were interpreted to represent intrauterine adhesions (IUA). Histologic examination of endometrial tissue obtained by curettage for lysis of IUA revealed endometrial carcinoma. The purpose of this report is to alert physicians to the possibility of endometrial adenocarcinoma when filling defects are demonstrated by HSG in young patients with prolonged anovulatory primary infertility.

Three patients (Ch. S., M. N., and R. E.), aged 32, 34, and 31, respectively, underwent HSG as part of an infertility workup. The patients had been oligomenorrheic since menarche and had anovulation and primary infertility of 10 to 13 years' duration. They did not conceive after multiple courses of Clomid and gonadotropin therapy.

HSG revealed markedly irregular uterine cavities with multiple filling defects (Fig. 1A) interpreted to represent IUA. All three underwent curettage for lysis of IUA. Histologic examination of the endometrium showed well-differentiated endometrial adenocarcinoma (Fig. 1B). They were treated by total abdominal hysterectomy and bilateral adnexectomy. Metastatic foci in the ovaries were found in one patient (R. E.) and she received postoperative external pelvic radiotherapy by <sup>60</sup>Co. All three patients are alive and well 8, 3, and 2 years, respectively, after diagnosis.

Endometrial curettage or biopsy, once part of the workup in infertility patients, is less frequently performed today because information concerning ovulation may be obtained by other means. HSG is thus often performed in patients with prolonged anovulation and infertility without documentation of the histologic nature of the endometrium. The pattern of

IUA on the x-ray film is very similar to the one obtained in endometrial adenocarcinoma showing irregular filling defects in the uterine cavity. Because of the infrequency of endometrial adenocarcinoma in young women, the awareness of this possibility is low and when filling defects are demonstrated by HSG a diagnosis of IUA is made erroneously.

Routine HSG in endometrial adenocarcinoma patients performed in some institutions<sup>1, 2</sup> has not so far gained common acceptance because of the presumed potential hazard of disease spread. Although the HSG in our patients has apparently not adversely affected the prognosis, it seems advisable to obtain cytologic or histologic information on the nature of the endometrium in young patients with anovulation and primary infertility of prolonged duration prior to the performance of HSG. On the other hand, when intrauterine filling defects are demonstrated in such patients without documentation of the nature of the endometrium, the possibility of endometrial carcinoma should be kept in mind.

#### REFERENCES

- Schwartz, P. E., Kohorn, E. I., Knowlton, A. H., and Mcl. Morris, J.: Routine use of hysterography in endometrial carcinoma and postmenopausal bleeding, Obstet. Gynecol. 45:378, 1975.
- Anderson, B., Marchant, D. J., Munzenrider, J. E., Moore, J. P., and Mitchell, G. W.: Routine non-invasive hysterography in the evaluation and treatment of endometrial carcinoma. Gynecol. Oncol. 4:374, 1976.

#### **ITEMS**

#### Infections in Obstetric Patients

The Department of Gynecology and Obstetrics of The Johns Hopkins University School of Medicine will present a continuing education course, entitled "Infections in Obstetric Patients," October 23-25, 1980.

For further information contact: Program Coordinator, Johns Hopkins University, 22 Turner Auditorium Bldg., 720 Rutland Ave., Baltimore, Maryland 21205.

#### Postgraduate Seminars

The Department of Obstetrics-Gynecology, University of Miami, announces the 1980-1981 Postgraduate Seminars:

- 1. Ultrasound Seminar, Doral Beach Hotel, December 10-14, 1980.
- 2. Ob-Gyn Cruise Seminar (Gynecologic Endocrinology), Aboard the S.S. Doric, January 3-12, 1981.
- 3. Ob-Gyn Caribbean Seminar, location to be announced, February (tba).
- 4. Ob-Gyn Cruise Seminar (Gynecologic Surgery and Oncology), aboard the S.S. Doric, March 20-30, 1981.

For information contact: Department of Obstetrics and Gynecology, University of Miami School of Medicine, P. O. Box 016960 (R-116), Miami, Florida 33101.

#### Adolescent Health: Crossing the Barriers

The Division of Pediatric Cardiology, the Department of Psychiatry, the Division of Health Education of The Johns Hopkins Medical Institutions, will present a continuing education conference, entitled "Adolescent Health: Crossing the Barriers," November 17-19, 1980, in Baltimore, Maryland.

For further information contact: Program Coordinator, Johns Hopkins University, 22 Turner Auditorium, 720 Rutland Ave., Baltimore, Maryland 21205.

#### Meetings sponsored by Perinatal Resources, Inc.

Perinatal Resources, Inc., announces two meetings. The first, "Obstetrics, Gynecology, and Endocrinology," will be held January 29–February 1, 1981, at the MGM Hotel, Las Vegas, Nevada. The second, "Update on Endocrinology, High Risk Obstetrics, and Gynecologic Surgery," will be held March 12-15, 1981, at the

Orlando Hyatt House, Kissimmee, Florida (Disney World).

For information write: Julie Zuspan, Program Coordinator, Perinatal Resources, Inc., Gibraltar House, 2400 Coventry Road, Columbus, Ohio 43221.

#### Ninth Annual Conference on Psychosomatic Obstetrics and Gynecology

The Ninth Annual Conference on Psychosomatic Obstetrics and Gynecology, sponsored by the American Society for Psychosomatic Obstetrics and Gynecology, will be held at the Temple University Conference Center, Philadelphia, Pennsylvania, March 25-28, 1981. Papers should be submitted to David D. Youngs, M.D., 131 Chadwick St., Portland, Maine 04102.

Information may be obtained from Raphael S. Good, M.D., President, Department of Psychiatry (D29), P. O. Box 016960, Miami, Florida 33101; or John F. Steege, M.D., Secretary, Department of Obstetrics and Gynecology, Duke University Medical Center, Box 3253, Durham, North Carolina 27710.

#### Fourth Reinier de Graaf Symposium

The Fourth Reinier de Graaf Symposium, "Follicular Maturation and Ovulation," will be held August 20-22, 1981, at Catholic University, Nijmegen, The Netherlands. The deadline for submission of abstracts is April 1, 1981.

Further details, including abstract, registration, and accommodation forms, may be obtained from: Professor R. Rolland, Fourth Reinier de Graaf Symposium Secretariat, Department of Obstetrics and Gynecology, St. Radboud University Hospital, 6500 HB Nijmegen, The Netherlands.

#### Lalor Foundation Research Fellowship Program for 1981

The Lalor Foundation has announced its 1981 program of postdoctorate grants for research in special areas of mammalian reproductive physiology.

The Foundation will make grants up to \$16,000 each to qualified tax-exempt institutions for conduct of approved projects up to one year. Foreign institutions can in general achieve similar eligibility.

The applicant institution has the obligation and freedom to make its own designation of a Lalor Fellow

for conduct of the research from among its own personnel or elsewhere. The Fellow designated should have achievement at least equivalent to the Ph.D. or M.D. degree. Upper age limit is 35 years.

Applications are restricted to research projects in female mammalian reproductive physiology bearing on (a) cervical and uterine physiology and phenomena of basic or clinical relevance to pregnancy interruption, particularly respecting second-trimester terminations or terminations emanating from impaired fetal environment and development, and (b) areas of pregnancy management which include basic or development work respecting induction of immunological controls, application of recombinant techniques of either genetic or pharmacologic character, and comparative physiology within other phylae that may give leads toward gestational controls in the human.

Forms and details for institution application are available from the Lalor Foundation, 3801 Kennett Pike, Bldg. B-108, Wilmington, Delaware 19807. Deadline for filing is January 15, 1981. Appointments will be announced March 15, 1981.

#### **Prevention and Treatment of Birth Defects**

The Council for Continuing Education Inc., in conjunction with the March of Dimes, is holding a one day meeting, November 12, 1980, in Saddlebrook, New Jersey at the Holiday Inn. The topic is "Prevention and Treatment of Birth Defects."

For information and to register contact: C. C. E., c/o C. Stokamer, 749 Howard St., Teaneck, New Jersey 07666.

#### Medical and Surgical Complications of Pregnancy

The Department of Obstetrics and Gynecology and The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY) announces a postgraduate course, "Medical and Surgical Complications of Pregnancy," to be held December 11 and 12, 1980, 9:00 AM to 5:00 PM (two sessions). This course will be given at the Mount Sinai Medical Center, New York, New York.

Apply to: Director, The Page and William Black Post-Graduate School of Medicine, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, New York 10029.

#### Tenth Annual Review Course in Obstetrics and Gynecology

The Tenth Annual Review Course in Obstetrics and Gynecology will be held January 26-30, 1981, at The Pasadena Hilton, Pasadena, California. The course will be presented by the University of Southern California School of Medicine Postgraduate Division and the Department of Obstetrics and Gynecology.

Direct inquiries to: Associate Dean, USC School of Medicine Postgraduate Division, 2025 Zonal Ave., KAM 307, Los Angeles, California 90033.

#### International Reproductive Health Seminar

The IPARC International Population and Reproduction Council, Inc., presents the Miami-Nassau Meeting, to be held April 21-25, 1981.

For further information write: IPARC Human Development Program, Inc., 1942 N.E. 151 St., North Miami, Florida 33162.

#### Fourth Annual Mid-Winter Symposium in Obstetrics and Gynecology

The Fourth Annual Mid-Winter Symposium in Obstetrics and Gynecology will be held February 25-27, 1981, at the Scottsdale Hilton Hotel, Scottsdale, Arizona. It is cosponsored by the Phoenix Obstetrics and Gynecology Society and the Department of Obstetrics and Gynecology, Maricopa County General Hospital.

For information contact: The Secretary, Phoenix OB/GYN Society, 333 E. Virginia, Suite 222, Phoenix, Arizona 85004.

#### Gynecologic Pathology for the Clinician

A postgraduate winter review course, "Gynecologic Pathology for the Clinician," will be held February 10-13, 1981, at Big Sky, Montana. This course is offered by the Department of Obstetrics and Gynecology of the University of Vermont and the Departments of Pathology and Obstetrics and Gynecology of the Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec, Canada. It is designed for both the clinician and the pathologist with emphasis on current pathogenetic and diagnostic concepts of gynecologic disorders and advances in their outpatient diagnosis. The faculty includes: J. Belinson, M.D., A. Ferenczy, M.D., M. M. Gelfand, M.D., R. M. Richart, M.D., Stanley Robboy, M.D., and Donald Woodruff, M.D. This course is approved for 22 credit hours in the American Medical Association, Category I, and for 22 cognates by the American College of Obstetricians and Gynecologists.

For application contact: Dr. A. Ferenczy, Department of Pathology, The Sir Mortimer B. Davis Jewish General Hospital, 3755 Côte Ste. Catherine Road, Montreal, Quebec, Canada H3T 1E2.

#### Current Optimum Strategies for Clinical Cancer Chemotherapy

A symposium, entitled "Current Optimum Strategies for Clinical Cancer Chemotherapy," sponsored by the Chemotherapy Foundation, will be held October 22, 23, and 24, 1980, at the Barbizon Plaza Hotel in New York, New York. It will be presented by The Division of Medical Oncology, The Department of Neoplastic Diseases and The Page and William Black Post-Graduate School of the Mount Sinai School of medicine (CUNY).

For information write to: Director, The Page and William Black Post-Graduate School of Medicine, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, New York 10029.

#### Infections in the OB/GYN Patient

"Infections in the OB/GYN Patient" will be presented October 25, 1980, from 8:30 AM to 4:00 PM, at the Teaching Center Auditorium, Long Island Jewish-Hillside Medical Center, New Hyde Park, New York. The program is sponsored by the Department of Obstetrics and Gynecology, Long Island Jewish-Hillside Medical Center, New Hyde Park, New York.

For further information contact: Continuing Education Coordinator, Long Island Jewish-Hillside Medical Center, New Hyde Park, New York 11042.

#### **Combined Annual Scientific Sessions**

The Combined Annual Scientific Sessions of the Society for Clinical Trials and the Eighth Annual Symposium for Coordinating Clinical Trials will be held May 11-13, 1981, in San Francisco, California. The Sessions will focus on the design, organization, management, and analyses of clinical trials. Abstracts must be *received* by January 1, 1981.

For information write to: Christian R. Klimt, M.D., Secretary, Society for Clinical Trials, Inc., 600 Wyndhurst Ave., Baltimore, Maryland 21210.

#### Pediatric and Adolescent Gynecology

The Department of Obstetrics and Gynecology and The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY) announce a postgraduate course, "Pediatric and Adolescent Gynecology, to be presented November 13 and 14, 1980.

Apply to: Director, The Page and William Black Post-Graduate School of Medicine, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, New York 10029.

#### Office Gynecology for Primary Physicians

"Office Gynecology for Primary Physicians" will be presented October 16-17, 1980, in Seattle, Washington, at the Museum of History and Industry. It is sponsored by the Washington State Medical Association and the University of Washington School of Medicine, Department of Obstetrics and Gynecology, Division of Continuing Medical Education.

For information write: University of Washington School of Medicine, Division of Continuing Medical Education, E-303 HSB, SC-50, Seattle, Washington 98195.

## Fourteenth Annual Postgraduate Course in Gynecologic Pathology, Cytogenetics, and Endocrinology

The Department of Gynecology and Obstetrics at The Medical College of Wisconsin will present the Fourteenth Annual Postgraduate Course in Gynecologic Pathology, Cytogenetics, and Endocrinology at the Pfister Hotel and Tower, Milwaukee, Wisconsin, on January 15-21, 1981. The six-day course has been extended to include a complete up-to-date review of endocrinology and cytogenetics in addition to a thorough résumé of gynecologic pathology. The course, which is limited to 150 registrants, is designed primarily as a postgraduate refresher course for residents, practitioners, and specialists desiring a current review of the pathology of the reproductive tract. Microscopes and a select group of microscopic slides will be available by special request along with special consultation and microscopic instructions by faculty. Space limitation requires registration for the entire course. This course is approved for 42 cognates, Formal Learning, by The American College of Obstetricians and Gynecologists and meets the criteria for 42 hours of credit in Category I, Physicians Recognition Award of the American Medical Association. A \$475.00 enrollment fee will include 68 selected 35 mm slides for all participants. The registration fee is nonrefundable. Among the guest faculty will be: H. W. Jones, Jr., M.D., Georgeanna S. Jones, M.D., J. D. Woodruff, M.D., and Robert Young, M.D. (NCI).

For further details and registration, write to: Richard F. Mattingly, M.D., The Medical College of Wisconsin, 8700 West Wisconsin Ave., Milwaukee, Wisconsin 53226.

# clinical ANEW BOOK! gynecologic oncology

By Philip J. DiSaia, M.D. and William T. Creasman, M.D.

This new book provides valuable guidelines for the diagnosis, treatment, and clinical management of common gynecologic malignancies. Its concise yet thorough coverage makes it a convenient reference source for the busy practitioner or for residents studying for the OB/GYN Boards. Key features include:

- Drs. Disaia and Creasman discuss current management methods as well as their own proven and preferred treatment suggestions
- chapters present information on etiology, pathological evaluation, diagnosis, clinical presentation, treatment and management, and recurrent disease
- discussions emphasize individualization

- of patient management
- chapters of special interest: cancer in pregnancy breast disease general aspects of tumor immunology adrenocarcinoma of the endometrium
- a glossary of terms for tumor immunology and an appendix containing information on F.I.G.O. staging and basic aspects of gynecologic radiotherapy are included
- a wealth of illustrations, tables, and charts depict clinical principles

Order your on-approval copy today and examine it for 30 days with no obligation!
October, 1980. Approx. 464 pages, 178 illustrations. About \$29.50.

# You'll want this book on hand.

To order your 30-day on-approval copies, CALL US!
Dial toll-free (800) 325-4177, ext. 10. In Missouri,
call collect (314) 872-8370, ext. 10 during our regular
business hours.

Master Card, VISA, or COD, goognested.

MasterCard, VISA, or C.O.D. accepted.

Price subject to change.

TIMES MIRROR

THE C. V. MOSBY COMPANY

11830 WESTLINE INDUSTRIAL DRIVE
ST. LOUIS, MISSOURI 63141

## INDEX TO ADVERTISERS

Appleton-Century-Crofts  Text	41	Merck, Sharp & Dohme Urecholine 35, 3	16
		55, 5	O
Ayerst Laboratories		Oaklawn Hospital	
Premarin1	6, 17, 18	Opportunity Available 4	0
Bradford & Kalston, M.D., P.A.			
Opportunity Available	38	Ortho Pharmaceutical Corporation Ortho-Novum 1/35 12, 13, 1	4
Burroughs Wellcome			
Empirin c Codeine	4	Parke-Davis Division of Warner-Lambert Co.	0
		Loestrin 28, 29, 30 Tabron 2	
Carnation Company			
- Instant Nonfat Dry Milk	10	D. H. H.	
		Prime Health Opportunity Available4	0
Centerville Medical Group		Opportunity Available 40	)
Opportunity Available	40		
		Purdue Frederick Company, The	
		Senokot	8
College of Physicians & Surgeons of Columbia			
University Postgraduate Course	10		
Postgraduate Course	42	Sandoz	
		Parlodel 25, 26, 2	7
Dorsey Laboratories			
Bellergal-S Third Cover, Fourt	th Cover		
		Karl Storz Endoscopy-America, Inc.	
		Laparoscope	5
Fancee Free Mfg. Company		Tubul Steritization 3	
Maternity Intimate Apparel	39		
		Syntex	
Genesee Health Service Medical Group		Norinyl $1 + 35$ Second Cover, 1, 2	2
Opportunity Available	42		
	Lati		
	1947	United States Army	
Hospital Corporation of America		Recruitment 3	7 •
Opportunity Available	42		
		The second secon	
Ives Laboratories Inc.		University of California, Los Angeles	,
Synalgos-DC	33	Opportunity Available 38	,
3M		University of Florida College of Medicine, The	
Steri-Strip Skin Closures	3	Opportunity Available 40	)
Mead Johnson Pharmaceutical Division		University of Utah	
Ovcon-35	43 44	Opportunity Available 39	)
	_ 10, 11		
MedaSonics, Inc.		Wyeth Laboratories	
Fetal Pulse Detector	39	Lo/Ovral22, 23, 24	+
			•

# CLINICAL BIOSTATISTICS:

# here's why you'll benefit from this book

- authoritative articles from <u>Clinical Pharmacology and</u> Therapeutics
- clear and easy-to-read explanations of essential statistical concepts
- provocative insights into the common sense and science behind statistical data

#### **CLINICAL BIOSTATISTICS**

This unique book critically examines the entire field of clinical biostatistics. It presents a series of original articles that first appeared over a five year period in *Clinical Pharmacology and Therapeutics*. Widespread reader acclaim and the timeliness of the subject prompted publication of the essays into convenient book form.

The essays are logically arranged into 29 chapters and organized into five major sections, each preceded by brief commentary written especially for the book. You'll find informative discussions on the diverse statistical techniques used in medical practice and research; research and design problems; presentation of data; and methods of data analysis. Dr. Feinstein has reorganized his original articles to provide you with a completely current guide to the biostatistics used in both clinical and investigative situations. He also offers valuable insights into topics either totally neglected or inadequately covered in conventional texts. Throughout, discussions are written in lively prose style, which makes the subject both interesting to read and easy-to-understand. Why not benefit from Dr. Feinstein's expert guidance firsthand—order your copy of CLINICAL BIOSTATISTICS today!

By **Alvan R. Feinstein**, M.D., 1977, 468 pages plus FM I-XIV, 6-7/8" x 10", 10 illustrations. Price, \$21.50

#### **ORDER BY PHONE!**

Call toll free (800) 325-4177 ext. 10. In Missouri call collect—(314) 872-8370 ext. 10 during normal business hours.

A80794

Price effective in U.S.A. only.



THE C V MOSBY COMPANY 11830 WESTLINE INDUSTRIAL DRIVE ST LOUIS MISSOURI 63141

## BELLERGAL-S TABLETS

Composition: Each Bellergal-S Tablet contains: phenobarbital, USP, central sedative (Warning: May be habit forming), 40.0 mg; Gynergen (ergotamine tartrate, USP) sympathetic inhibitor, 0.6 mg; Bellafoline (levorotatory alkaloids of belladonna, as malates) parasympathetic inhibitor, 0.2 mg.

Properties and Therapeutics: Based on the concept that functional disorders frequently involve hyperactivity of both the sympathetic and parasympathetic nervous, systems, the ingredients in Bellergal are combined to provide a balanced preparation designed to correct imbalance of the autonomic nervous system. The integrated action of Bellergal is effected through the combined administration of ergotamine and the levorotatory alkaloids of belladonna, specific inhibitors of the sympathetic and parasympathetic respectively, reinforced by the synergistic action of phenobarbital in dampening the cortical centers.

**Indications:** Bellergal is employed in the management of disorders characterized by nervous tension and exaggerated autonomic response:

<u>Menopausal disorders</u> with hot flashes, sweats, restlessness and insomnia.

<u>Cardiovascular disorders</u> with palpitation, tachycardia, chest oppression and vasomotor disturbances.

<u>Gastrointestinal disorders</u> with hypermotility, hypersecretion, "nervous stomach," and alternately diarrhea and constipation.

Genitourinary - uterine cramps, etc.

Premenstrual tension.

Interval treatment of <u>recurrent</u>, <u>throbbing</u> headache.

Contraindications: Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis, third trimester of pregnancy and glaucoma. Hypersensitivity to any of the components.

**Precautions:** Even though the ergotamine tartrate content of this product is extremely low and untoward effects have been rare and insignificant, caution should be exercised if large or prolonged dosage is contemplated, and physicians should be alert to possible peripheral vascular complications in patients highly sensitive to ergot. Due to presence of a barbiturate, may be habit forming.

**Side Effects:** Blurred vision, dry mouth, flushing, drowsiness occur rarely.

**Dosage:** Bellergal-S Tablets: One in the morning and one in the evening.

**How Supplied:** Bellergal-S Tablets (compressed, scored tablets of tricolored pattern: dark green, orange and light lemon yellow) in bottles of 100.



NONHORMONAL therapy for menopausal vasomotor instability is receiving renewed attention.



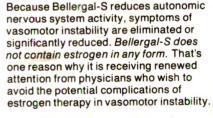
# BELLERGALS

# TABLETS

Each Bellergal-S Tablet contains: phenobarbital, USP central sedative (Warning: May be habit forming), 40.0 mg: Gynergen® (ergotamine tartrate, USP) sympathetic inhibitor, 0.6 mg: Bellafoline® (levorotatory alkaloids of belladonna, as malates) parasympathetic inhibitor, 0.2 mg.



Long clinical experience has established the effectiveness of Bellergal-S Tablets in managing menopausal disorders characterized by exaggerated autonomic response—hot flashes, sweats, restlessness, and insomnia.







So when estrogen therapy is undesirable... prescribe Bellergal-S Tablets.

Please see prescribing information on an adjoining page.

© 1979 Dorsey Laboratories/Division of Sandoz, Inc.

October 15, 1980 volume 138, number 4

# Imerican Journal OF OBSTETRICS AND GYNECOLOGY

Copyright © 1980 by The C. V. Mosby Company

Editor in Chief
JOHN I. BREWER

Editors

FREDERICK P. ZUSPAN · E. J. QUILLIGAN

Associate Editor
ALBERT B. GERBIE

Emeritus Editors
HOWARD C. TAYLOR, JR. · ALLAN C. BARNES

#### Official Publication

AMERICAN GYNECOLOGICAL SOCIETY

AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA
SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
PACIFIC COAST OBSTETRICAL AND GYNECOLOGICAL SOCIETY
AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY
SOCIETY FOR GYNECOLOGIC INVESTIGATION

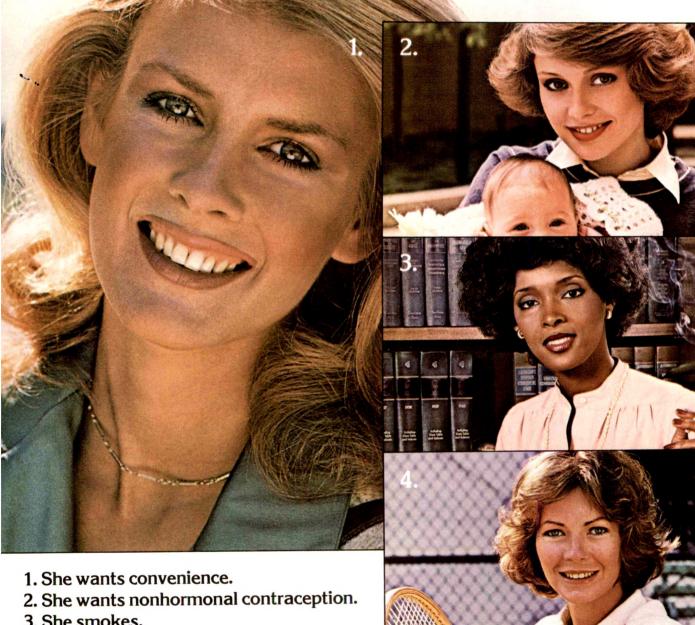


Published by

THE C. V. MOSBY COMPANY St. Louis, Missouri 63141



# Four kinds of contraceptive priorities.



- 3. She smokes.
- 4. She is over 35.

## Cu-7/ Tatum-

(intrauterine copper contraceptives)

#### **Answer their** contraceptive priorities...

- 1. For the contemporary woman who wants freedom from rigid schedules, the copper IUD is a logical choice because of its inherent convenience.
- 2. For the new mother who wants to space her family the copper I(ID) has no effect on lactation.

Therefore, the postpartum period may be an esp cially opportune time to insert a Cu-7 or Tatum-T, providing involution has occurred.

- 3. For the woman—of any age—who smokes, the copper IUD produces no problems in association with smoking.
- **4.** For the woman who has passed the Pill years, but who still wants highly effective and reversible contraception, the copper IUDs are a logical choice.

Intrauterine contraception is not appropriate for all women. See complete prescribing information prior to use.

## Cu-7/ Tatum-T

#### (intrauterine copper contraceptives)

**Description:** The Cu-7 has coiled around the vertical limb 89 mg. of copper wire providing approximately 200 mm² of exposed copper surface area. The Tatum-T has coiled around the vertical limb 120 mg. of copper wire providing approximately 210 mm² of exposed copper surface area

Contraindications: Not to be inserted when any of the following conditions exist: pregnancy or suspicion of pregnancy; abnormalities of the uterus resulting in distortion of the uterine cavity, acute pelvic inflammatory disease or history of repeated pelvic inflammatory disease, postpartum endometritis or infected abortion in the past three months; known or suspected uterine or cervical disease such as hyperplasia or carcinoma including unresolved, abnormal "Pap" smear; vaginal bleeding of unknown etiology; untreated acute cervicitis until infection is controlled; diagnosed Wilson's disease; known or suspected allergy to copper; previous ectopic pregnancy; significant anemia; and valvular heart disease, leukemia, or use of chronic corticosteroid therapy

Warnings

Pregnancy: (a) Long-term effects. The long-term effects on the offspring of the presence of

copper in the uterus when pregnancy occurs are unknown.

(b) Septic abortion. Reports have indicated an increased incidence of septic abortion. (b) <u>Septic abortion</u>. Reports have indicated an increased incidence of septic abortion associated in some instances with septicemia, septic shock and death in patients becoming pregnant with an IUD in place. Most of these reports have been associated with the mid-trimester of pregnancy. In some cases, the initial symptoms have been insidious and not easily recognized. If pregnancy should occur with a Cu-7 or Tatum-Tin situ, the IUD should be removed if the thread is visible or, if removal proves to be or would be difficult, interruption of the pregnancy should be considered and offered to the patient as an option, bearing in mind that the risks associated with an elective abortion increase with nest-tained and

the pregnancy should be considered and offered to the patient as an option, bearing in mind that the risks associated with an elective abortion increase with gestational age.

(c) Continuation of pregnancy. If the patient chooses to continue the pregnancy and the Cu-7 or Tatum-T remains in situ, she must be warned of increased risk of spontaneous abortion and increased risk of sepsis, including death. The patient must be closely observed and advised to report immediately all abnormal symptoms, such as flu-like syndrome, fever, abdominal cramping and pain, bleeding, or vaginal discharge, because generalized symptoms of septicemia may be insidious.

2. Ectopic pregnancy: (a) Pregnancy which occurs with an IUD in situ is more likely to be ectopic than pregnancy occurring without an IUD. Therefore, patients who become pregnant while using a Cu-7 or Tatum-T should be carefully evaluated for the possibility of ectopic

(b) Special attention should be directed to patients with delayed menses, slight metrorrhagia and/or unilateral pelvic pain, and to those patients who wish to interrupt a pregnancy occurring in the presence of a Cu-7 or Tatum-T, to determine whether ectopic

pregnancy has occurred

Pelvic infection: An increased risk of pelvic inflammatory disease associated with the use of 3. <u>Pelvic infection</u>: An increased risk of pelvic inflammatory disease associated with the use of IUDs has been reported. While unconfirmed, this risk appears to be greatest for young women who are nulliparous and/or who have multiple sexual partners. Salpingitis can result in tubal damage and occlusion, thereby threatening future fertility. Therefore, it is recommended that patients be taught to look for symptoms of pelvic inflammatory disease. The decision to use an IUD in a particular case must be made by the physician and patient with consideration of a possible deleterious effect on future fertility. Pelvic infection may occur with a Cu-7 or Tatum-T in situ and at times result in the development of tubo-ovarian abscesses or general peritonitis. The symptoms of pelvic infection include: new development of menstrual disorders (prolonged or heavy bleeding).

development of tubo-ovarian abscesses or general peritoritis. The symptoms of pelvic infection include: new development of menstrual disorders (prolonged or heavy bleeding) abnormal vaginal discharge, abdominal or pelvic pain, dyspareunia, fever. The symptoms are especially significant if they occur following the first few cycles after insertion. Appropriate aerobic and anaerobic bacteriologic studies should be done and antibiotic therapy initiated promptly. If the infection does not show marked clinical improvement within 24 to 48 hours, the Cu-7 or Tatum-T should be removed and continuing treatment reassessed on the being frequent of synthesis and continuing treatment reassessed. on the basis of results of culture and sensitivity tests.

- 4. Embedment: Partial penetration or lodging of the Cu-7 or Tatum-T in the endometrium or myometrium can result in difficult removal. This may occur more frequently in smaller uteri. See removal instructions
- 5 Perforation: Partial or total perforation of the uterine wall or cervix may occur, usually during insertions into patients sooner than two months after abortion or delivery, or in uterine cavities too small. The possibility of perforation must be kept in mind during insertion and at the time of any subsequent examination. If perforation occurs, laparotomy or laparoscopy should be performed as soon as medically feasible and the Cu-7 or Tatum-T removed Abdominal adhesions, intestinal penetration, intestinal obstruction, and local inflammatory reaction with abscess formation and erosion of adjacent viscera may result if the Cu-7 or Tatum-T is left in the peritoneal cavity.
- 6. Medical diathermy: The use of medical diathermy (short-wave and microwave) in a patient with a metal-containing IUD may cause heat injury to surrounding tissue. Therefore, medical diathermy to the abdominal and sacral areas should not be used on patients using a Cu-7 or
- 7. Effects of copper: Additional amounts of copper available to the body from the Cu-7 or Tatum-T may precipitate symptoms in women with undiagnosed Wilson's disease. The incidence of Wilson's disease is 1 in 200,000.

- 1.-Patient counseling. Prior to insertion the physician, nurse, or other trained health professional must provide the patient with the Patient Brochure. The patient should be given the opportunity to read the brochure and discuss fully any questions she may have concerning the Cu-7 or Tatum-Tas well as other methods of contraception.
- 2. Patient evaluation and clinical considerations. (a) A complete medical history should be obtained to determine conditions that might influence the selection of an IUD. A physical examination should include a pelvic examination, "Pap" smear, gonorrhea culture and, if indicated, appropriate tests for other forms of venereal disease. The physician should betermine that the patient is not pregnant.

(b) The uterus should be carefully sounded prior to insertion to determine the degree of patency of the endocervical canal and internal os, and the direction and depth of the uterine

ca\*ity. Exercise care to avoid perforation with the sound. DO NOT USE THE INSERTION INSTRUMENT AS A SOUND. In occasional cases, severe cervical stenosis may be encountered. Do not use excessive force to overcome this resistance.

(c) The uterus usually sounds to a depth of 6 to 8 cm. Insertion into a uterine cavity measuring less than 6.5 cm. by sounding may increase the incidence of pain, bleeding, partial or complete expulsion, perforation, and possibly pregnancy.

(d) To reduce the possibility of insertion in the presence of existing undetermined pregnancy, the optimal time for insertion is the latter part of the menstrual flow or one or two days thereafter. The Cu-7 or Tatum-1 should not be inserted post partum or post abortion until involution of the uterus is complete. The incidence of perforation and expulsion is greater if involution of the uterus is complete. The incidence of perforation and expulsion is greater if involution is not complete.

It is, however, necessary to place the Cu-7 or Tatum-Tas high as possible within the utaine cavity to help avoid partial or complete expulsion that could result in pregnancy.

Physicians are cautioned that it is imperative for them to become thoroughly familiar with the instructions for use before attempting placement of the Cu-7 or Tatum-T.

(e) IUDs should be used with caution in those patients who have anemia or a history of menorrhagia or hypermenorrhea. Patients experiencing menorrhagia and/or metrorrhagia fcllowing IUD insertion may be at risk for the development of hypochromic microcytic nemia. Also, IUDs should be used with caution in patients receiving anticoagulants or having a coagulopathy.

(f) Syncope, bradycardia or other neurovascular episodes may occur during insertion or

removal of IUDs, especially in patients with a previous disposition to these conditions.

(g) Patients with valvular or congenital heart disease are more prone to develop subacute tacterial endocarditis than patients who do not have such disease. Use of an IUD in these

catients may represent a potential source of septic emboli.

(h) Use of an IUD in patients with acute cervicitis should be postponed until proper treatment has cleared up the infection.

(i) Since the Cu-7 or Tatum-T may be partially or completely expelled, patients should be reexamined and evaluated shortly after the first postinsertion menses, but definitely within three months after insertion. Thereafter annual examination with appropriate medical and boratory evaluation should be carried out. The Cu-7 or Tatum-T should be replaced every

(j) The patient should be told that some bleeding or cramping may occur during the first few weeks after insertion, but if these symptoms continue or are severe she should report them to her physician. She should be instructed on how to check after each menstrual period to make certain that the thread still protrudes from the cervix and cautioned that there is no contraceptive protection if the Cu-7 or Tatum-T has been expelled. She should also be cautioned not to dislodge the Cu-7 or Tatum-T by pulling on the thread. If a partial expulsion occurs, removal is indicated and a new Cu-7 or Tatum-T may be inserted. The patient should be told to return within three years for removal of the Cu-7 or Tatum-T and for replacement if

(k) A copper-induced urticarial allergic skin reaction may develop in women using a copper-containing IUD. If symptoms of such an allergic response occur, the patient should be instructed to tell the consulting physician that a copper-containing device is being used.

(i) The Cu-7 or Tatum-T should be removed for the following medical reasons: menorrhagia and/or metrorrhagia producing significant anemia; uncontrolled pelvic infection; intractable

pain often aggravated by intercourse, dyspareunia; pregnancy, if the thread is visible; endometrial or cervical malignancy; uterine or cervical perforation; or any indication of partial

(m) If the retrieval thread cannot be seen it may have retracted into the uterus or have been broken off, or the Cu-7 or Tatum-T may have been expelled. Localization usually can be made by feeling with a probe; if not, x-ray or sonography can be used. When the physician elects to recover a Cu-7 or Tatum-T with the thread not visible, the removal instructions should be considered.

(n) If any patient with a Cu-7 or Tatum-T suddenly develops overt clinical hepatitis or abnormal liver function tests, appropriate diagnostic procedures should be initiated

Adverse Reactions: Perforations of uterus and cervix have occurred. Perforation into the abdomen has been followed by abdominal adhesions, intestinal penetration, intestinal obstruction, local inflammatory reaction with abscess formation and erosion of adjacent viscera. Pregnancy has occurred with the Cu-7 or Tatum-T in situ and when either has been

partially or completely expelled.

The incidence of spontaneous abortion, when conception occurs with intrauterine devices in situ, appears to be increased over that in unprotected women. Insertion cramping, usually of no more than a few seconds' duration, may occur; however, some women may experience residual cramping for several hours or even days. Intermenstrual spotting or bleeding or

residual cramping for several hours or even days. Intermenstrual spotting or bleeding or prolonged or increased menstrual flow may occur.

Pelvic infection including salpingitis with tubal damage or occlusion has been reported. This may result in future infertility. Complete or partial expulsion of the Cu-7 or Tatum-T may sometimes occur, particularly in those patients with uteri measuring less than 6.5 cm. by sounding. Urticarial allergic skin reaction may occur. The following complaints have also been reported with IUDs although their relation to the Cu-7 or Tatum-T has not been restablished; amongstreager depress hexaches cervical experience cystic masses in established: amenorrhea or delayed menses, backaches, cervical erosion, cystic masses in the pelvis, vaginitis, leg pain or soreness, weight loss or gain, nervousness, dyspareunia, cystitis, endometritis, septic abortion, septicemia, leukorrhea, ectopic pregnancy, difficult removal, uterine embedment, anemia, pain, neurovascular episodes including bradycardia and syncope secondary to insertion, dysmenorrhea, and fragmentation of the IUD.

Clinical Efficacy: In clinical trials, use effectiveness was determined as follows for parous and nulliparous women, as tabulated by the life table method. (Rates are expressed as cumulative events per 100 women through 12, 24, and 36 months of use.)

Cu-7 experience encompasses 387,131 woman-months of use, including 12 months for 11,517 women, 24 months for 7,895, and 36 months for 3,661.

Tatum-T experience encompasses 236,060 woman-months of use in the United States and Canada, including 12 months for 8,232 women, 24 months for 4,247, and 36 months

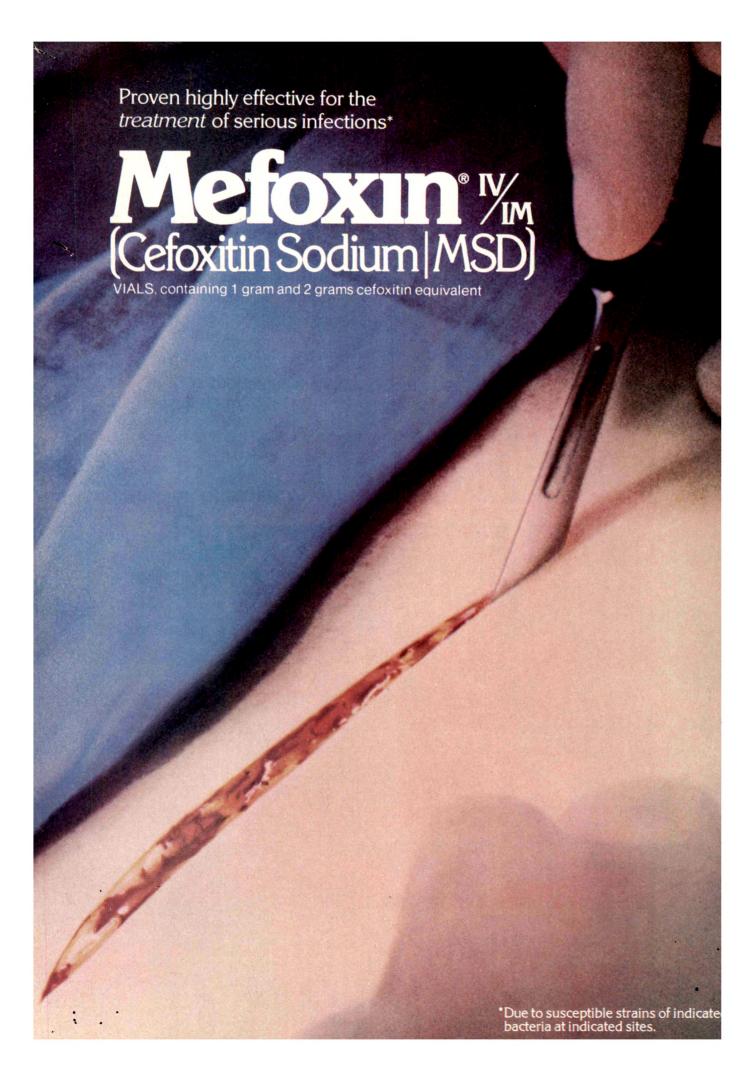
for 1,408.

Cumulative pregnancy rates were

	12 Mo Parous Nu			Months Nulliparous		Months Mulliparous
Cu-7	1.9	1.7	2.9	() 2.6	3.4	3.4
Tatum-T	3.0	2.1	149	455	6.0	5.8

**SEARLE** 

Searle Laboratories Division of Searle Pharma Box 5110, Chicago, Wirois



# for prophylaxis to reduce the incidence of certain postoperative infections complicating

GI surgery • Vaginal hysterectomy • Cesarean section =

Providing a broad spectrum—including Bacteroides fragilis

In controlled clinical trials, MEFOXIN<sup>®</sup> (Cefoxitin Sodium, MSD) reduced the incidence of certain postoperative infections

with use limited to a 24-hour period following the operative procedure.

Prophylactic administration should usually be stopped within 24 hours since continuing administration of any antibiotic increases the possibility of adverse reactions.

- †Perioperatively: Two grams administered intravenously or intramuscularly just prior to surgery (approximately ½ to 1 hour before the initial incision); then 2 grams every 6 hours for no more than 24 hours.
- ‡Cesarean-section patients: The first dose of 2 grams is administered intravenously as soon as the umbilical cord is clamped. The second and third doses should be given as 2 grams intravenously or intramuscularly 4 hours and 8 hours after the first dose. Subsequent doses may be given every 6 hours for no more than 24 hours.

For complete details on dosage and administration, see full prescribing information.

If there are signs of infection, specimens for culture should be obtained for the identification

of the causative organisms so that appropriate therapy may be instituted.

MEFOXIN (Cefoxitin Sodium, MSD) is contraindicated in patients who have shown hypersensitivity to cefoxitin and the cephalosporin group of antibiotics. Before therapy with MEFOXIN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefoxitin, cephalosporins, penicillins, or other drugs. This product should be given with caution to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to MEFOXIN occurs, discontinue the drug. Serious hypersensitivity reactions may require epinephrine and other emergency measures. Use of the drug in women of childbearing potential requires that the anticipated benefit be weighed against the possible risks.

For a brief summary of prescribing information, please see following page.



Indications and Usage: Treatment - Serious infections caused by susceptible strains of the designated microorganisms in the following

LOWER RESPIRATORY TRACT INFECTIONS, including pneumonia and lung abscess, caused by Streptococcus pneumoniae (formerly Diplococcus pneumoniae), other streptococci (excluding enterococci, e.g., Strep. faecalis), Staphylococcus aureus (penicillinase and nonpenicillinase producing), Escherichia coli, Klebsiella species, Hemophilus influenzae, and Bacteroides species.

GENITOURINARY INFECTIONS. Urinary tract infections caused by E. coli, Klebsiella species, Proteus mirabilis, indole-positive Proteus (i.e., P. morganii, P. rettgeri, and P. vulgaris), and Providencia species. Uncomplicated gonorrhea due to Neisseria gonorrhoeae. INTRA-ABDOMINAL INFECTIONS, including peritonitis and intra-abdominal abscess, caused by *E. coli, Klebsiella* species, *Bacteroides* 

species including the *B. fragilis* group,‡ and *Clostridium* species. GYNECOLOGICAL INFECTIONS, including endometritis, pelvic cellulitis, and pelvic inflammatory disease, caused by E. coli, N. gonor-rhoeae, Bacteroides species including the B. fragilis group,‡ Clostridium species, Peptococcus species, Peptostreptococcus species, and group B streptococci.

SEPTICEMIA caused by Strep. pneumoniae (formerly D. pneumoniae), Staph. aureus (penicillinase and non-penicillinase producing), E. coli, Klebsiella species, and Bacteroides species

including the *B. fragilis* group.‡
BONE AND JOINT INFECTIONS caused by *Staph. aureus* (penicil-

linase and non-penicillinase producing).
SKIN AND SKIN STRUCTURE INFECTIONS caused by Staph. aureus (penicillinase and non-penicillinase producing), Staph. epidermidis, streptococci (excluding enterococci, e.g., Strep. faecalis), E. coli, P. mirabilis, Klebsiella species, Bacteroides species including the B fragilis group,‡ Clostridium species, Peptococcus species, and Peptostreptococcus species.

Although appropriate culture and susceptibility studies should be performed, therapy may be started while awaiting these results. Cefoxitin is not active in vitro against most strains of Pseudomonas aeruginosa and enterococci (e.g., Strep. faecalis) and many strains of Enterobacter cloacae. Methicillin-resistant staphylococci are almost

uniformly resistant to cefoxitin. Prevention - Prophylactic use perioperatively (preoperatively, intraoperatively, and postoperatively) in surgical procedures (e.g., vaginal hysterectomy, gastrointestinal surgery) classified as contaminated or potentially contaminated or in patients in whom infection at the operative site would present a serious risk, e.g., prosthetic arthroplasty; intraoperatively (after umbilical cord is clamped) and postoperatively in

cesarean section.

MEFOXIN usually should be given 1/2 to 1 hour before the operation, which is sufficient time to achieve effective levels in the wound during the procedure. Prophylactic administration should usually be stopped within 24 hours since continuing administration of any antibiotic increases the possibility of adverse reactions but, in the majority of surgical procedures, does not reduce the incidence of subsequent infection. However, in patients undergoing prosthetic arthroplasty, it is recommended that MEFOXIN be continued for 72 hours after the surgical procedure. If there are signs of infection, specimens for culture should be obtained for the identification of the causative organism so that appropriate therapy may be instituted.

Contraindications: Previous hypersensitivity to cefoxitin and the

cephalosporin group of antibiotics.

Warnings: BEFORE THERAPY IS INSTITUTED, CAREFUL INQUIRY
SHOULD BE MADE TO DETERMINE PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN, CEPHALOSPORINS, PENICILLINS, OR

OTHER DRUGS. GIVE WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFOXITIN OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPH-RINE AND OTHER EMERGENCY MEASURES

Precautions: The total daily dose should be reduced in patients with transient or persistent reduction of urinary output due to renal insufficiency because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses. As with other antibiotics, prolonged use may result in overgrowth of nonsusceptible organisms; repeated evaluation of the patient's condition is essential. If superinfection occurs, take appropriate measures. Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Interference with Laboratory Tests — As with cephalothin, high concen-

trations (>100 mcg/ml) may interfere with measurement of serum and urine creatinine levels by the Jaffé reaction and produce false increases of modest degree in creatinine levels reported; serum samples should not be analyzed for creatinine if withdrawn within 2 hours of cefoxitin administration. A false-positive reaction for glucose in urine has been observed with CLINITEST reagent tablets.

Pregnancy—In women of childbearing potential, weigh anticipated benefit against possible risks.

Nursing Mothers - Cefoxitin is excreted in human milk in low concentrations

Infants and Children — Safety and efficacy in infants from birth to three months have not yet been established. In children three months and older, higher doses have been associated with increased incidence of eosinophilia and elevated SGOT.

Adverse Reactions: The most common adverse reactions have been local reactions following intravenous or intramuscular injection. Other adverse reactions have been encountered infrequently. Local Reactions - Thrombophlebitis with intravenous administration; pain, induration, and tenderness after intramuscular injections. Allergic Reactions - Rash, pruritus, eosinophilia, fever, and other allergic reactions. Gastrointestinal - Nausea, vomiting, and diarrhea. Blood-Transient eosinophilia, leukopenia, neutropenia, and hemolytic anemia; a positive direct Coombs test may develop in some individuals, especially those with azotemia. Liver Function — Transient elevations in SGÓT, SGPT, serum LDH, and serum alkaline phosphatase. Renal Function — Elevations in serum creatinine and/or blood urea

Note: In group A beta-hemolytic streptococcal infections, therapy should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated. Intramuscular injections should be well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel. The total daily dosage

in infants and children should not exceed 12 grams.

How Supplied: Sterile cefoxitin sodium in vials and infusion bottles containing 1 gram or 2 grams cefoxitin equivalent.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, PA 19486

#B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus Registered trademark of Ames Company, Division of Miles Laboratories, Inc.

## American Journal of Obstetrics and Gynecology

**Contents** 

Copyright © 1980 by The C. V. Mosby Company

October 15

1980

## Clinical opinion

## What can be done to prevent congenital toxoplasmosis?

357

Christopher B. Wilson, M.D., and Jack S. Remington, M.D. Stanford, California

## Gynecology

## Response to repetitive luteinizing hormone-releasing hormone stimulation in hypothalamic and pituitary disease

364

Anne Colston Wentz, M.D., and Richard N. Andersen, Ph.D. Memphis, Tennessee

(Contents continued on page 7)

Vol. 138, No. 4, October 15, 1980. The American Journal of Obstetrics and Gynecology is published semimonthly by The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141. POSTMASTER: Send address changes to above address.

1980 Annual subscription rates	U.S.A.	Foreign countries (surface mail) All regions	Region 1	Foreign countries (airmail)* Region 2	Region 3
Institutional† Individual‡	\$52.50 \$35.50	\$72.50 \$55.50	\$101.45 \$ 84.45	\$132.65 \$115.65	\$163.85 \$146.85
Student, resident‡	\$28.40	\$48.40	\$ 77.35	\$108.55	\$139.75

Single copies are \$4.50 postpaid. Remittances should be made by check, draft, or post office or express money order, payable to this JOURNAL.

\*Airmail breakdown—Domestic: First-class and Priority rates for the U.S. and possessions are available upon request. Region 1: Central America, islands, and mainland colonies of European countries in The Americas. Region 2: South America, Europe, Egypt, Africa (bordering the Mediterranean). Region 3: Asia, Australasia, Africa (other than Mediterranean), Middle East, Far East, The Pacific, U.S.S.R. (and constituent Republics).

†Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics; city, county, state, provincial, and national government bureaus and departments; and all commercial and private institutions and organizations.

‡Personal subscriptions and all student-rate subscriptions must be in the names of, billed to, and paid by individuals. All student-rate requests must indicate training status and name of institution.

Subscriptions may begin at any time.

Second-class postage paid at St. Louis, Missouri, and additional mailing offices. Printed in the U.S.A. Copyright © 1980 by The C. V. Mosby Company.

## DIAGNOSIS AND MANAGEMENT OF THE FETUS AND NEONATE AT RISK: A Guide for Team Care

By S. Gorham Babson, M.D.; Martin L. Pernoll, M.D.; and Gerda I. Benda, M.D.; with the assistance of Katherine Simpson, R.N.

New 4th Edition! Through three successful editions, you and your colleagues have depended on this reference for a comprehensive, down-to-earth view of perinatal care. This edition continues — and exceeds — that tradition of excellence. Stressing the team approach, it details the information you need to identify and manage the high risk mother, fetus and infant. Carefully updated sections:

- discuss diagnosis and management of the high risk fetus and neonate identification of high risk situations, congenital and genetic defects, electronic fetal monitoring and more
- explain serious obstetrical problems and the perinate malpresentation, diabetes, infection, cord accidents and very low birthweight
- explore specific neonatal problems respiratory, cardiovascular, hemotologic, metabolic and developmental disorders
- outline perinatal outcomes developmental prospects for the newborn and guidelines for regionalization of pediatric intensive care October, 1979. 358 pages, 99 illustrations. Price, \$21.95.

For even faster service, or if coupon has been removed, CALL US! Dial toll-free (800) 325-4177, ext. 10; in Missouri, call collect (314) 872-8370, ext. 10 during our regular business hours.

**AMS133** 

## Mosby keeps you informed

Mail this coupon today and you'll have 30 days to evaluate your selections.



THE C. V. MOSBY COMPANY 11830 WESTLINE INDUSTRIAL DRIVE ST. LOUIS, MISSOURI 63141

## OBSTETRICAL PRACTICE

Edited by Silvio Aladjem, M.D.; with 50 contributors.

A New Book! Logically organized into two parts — normal, and abnormal obstetrics — this easy-to-read volume contains authoritative, up-to-date information on key areas in obstetrics Among the topics examined in this well-illustrated text:

- the psychosomatic aspects of obsterics the factors determining a woman's coping mechanisms and the obstetrician's role in resolving problems during pregnancy and after
- the maternal-paternal-infant bonding relationship — methods professional can use to help the family deal with perinatal stresses and establish clos attachments
- infections in obstetrics viral, protozoal, fungal, and bacterial infections that challenge the physicial responsible for the health care of the pregnant woman and fetus
- management of cancer during pregnancy — the efficacious managemen of the patient with gynecologic or nongynecologic cancer

September, 1980. Approx. 992 pages, 415 illustrations. About \$29.95.

410 mastrations. 1100at \$27.75.
YES! I want to inspect an on-approval copy of the book(s) I've checked below.  Bill me Payment enclosed mastercard VISA
<ul> <li>DIAGNOSIS AND MANAGEMENT OF THE FETUS AND NEONATE AT RISK, 4th edition, (0415-X) \$21.95</li> <li>OBSTETRICAL PRACTICE (0114-2) \$29.95*</li> <li>MANAGEMENT OF JUVENILE DIABETES MELLITUS, 3rd edition, By Howard S. Traisman, (5020-8) \$39.50</li> <li>CLINICAL PERINATOLOGY, 2nd edition, Edited by Silvio Aladjem, Audrey K. Brown and Claude Sureau, (0103-7) \$49.50</li> <li>LECTURE NOTES ON OBSTETRICS, 4th edition, By G.V.P. Chamberlain, (B-1133-4) \$15.95*</li> <li>AMS133-031-03</li> </ul>
Name

Complete and mail to:

The C.V. Mosby Company 11830 Westline Industrial Drive St. Louis, Mo. 63141

## Contents continued from page 5

The standing cystometrogram	369
Stuart A. Weprin, M.D., and Frederick P. Zuspan, M.D., F.A.C.O.G.	
Columbus, Ohio	
	074
The effect of radical hysterectomy on bladder physiology	374
J. Peter Forney, M.D.	
Dallas, Texas	
the second defined changes in the	383
Temporal relationships between ovulation and defined changes in the	
concentration of plasma estradiol-17β, luteinizing hormone, follicle-stimulating	
hormone, and progesterone. I. Probit analysis	
World Health Organization, Task Force on Methods for the Determination of the Fertile Period,	
Special Programme of Research, Development and Research Training in Human Reproduction	
Malacoplakia of the female genital tract	391
A. Chalvardjian, B.A., M.D., F.R.C.P.(C.), L. Picard, M.D., R. Shaw, M.D., F.R.C.P.(C.),	
R. Davey, M.D., F.R.C.S.(C.), and J. D. Cairns, M.A., F.A.C.S., F.R.C.S.(C.)	
Toronto, Ontario, Canada	
Toronto, Cinario, Caraman	205
Para-aortic lymphocyst	395
Para-aortic lymphocyst  B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R.	395
	393
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R.	393
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D.	393
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida	393
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D.	393
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida  Obstetrics	399
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida  Obstetrics  Blind oxytocin challenge test and perinatal outcome	
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida  Obstetrics  Blind oxytocin challenge test and perinatal outcome  K. J. Staisch, M.D., J. R. Westlake, Ph.D., and R. A. Bashore, M.D.	
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida  Obstetrics  Blind oxytocin challenge test and perinatal outcome  K. J. Staisch, M.D., J. R. Westlake, Ph.D., and R. A. Bashore, M.D. Los Angeles, California	399
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida  Obstetrics  Blind oxytocin challenge test and perinatal outcome K. J. Staisch, M.D., J. R. Westlake, Ph.D., and R. A. Bashore, M.D. Los Angeles, California  Suppression of threatened premature labor by administration of cortisol and	
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida  Obstetrics  Blind oxytocin challenge test and perinatal outcome K. J. Staisch, M.D., J. R. Westlake, Ph.D., and R. A. Bashore, M.D. Los Angeles, California  Suppression of threatened premature labor by administration of cortisol and	399
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida  Obstetrics  Blind oxytocin challenge test and perinatal outcome  K. J. Staisch, M.D., J. R. Westlake, Ph.D., and R. A. Bashore, M.D. Los Angeles, California  Suppression of threatened premature labor by administration of cortisol and 17α-hydroxyprogesterone caproate: A comparison with ritodrine	399
<ul> <li>B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida</li> <li>Obstetrics</li> <li>Blind oxytocin challenge test and perinatal outcome</li> <li>K. J. Staisch, M.D., J. R. Westlake, Ph.D., and R. A. Bashore, M.D. Los Angeles, California</li> <li>Suppression of threatened premature labor by administration of cortisol and 17α-hydroxyprogesterone caproate: A comparison with ritodrine</li> <li>Antti Kauppila, Anna-Liisa Hartikainen-Sorri, Olli Jänne, Risto Tuimala, and Pentti A. Järvinen</li> </ul>	399
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida  Obstetrics  Blind oxytocin challenge test and perinatal outcome  K. J. Staisch, M.D., J. R. Westlake, Ph.D., and R. A. Bashore, M.D. Los Angeles, California  Suppression of threatened premature labor by administration of cortisol and 17α-hydroxyprogesterone caproate: A comparison with ritodrine  Antti Kauppila, Anna-Liisa Hartikainen-Sorri, Olli Jänne, Risto Tuimala, and Pentti A. Järvinen Oulu, Finland	399
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida  Obstetrics  Blind oxytocin challenge test and perinatal outcome  Κ. J. Staisch, M.D., J. R. Westlake, Ph.D., and R. A. Bashore, M.D. Los Angeles, California  Suppression of threatened premature labor by administration of cortisol and 17α-hydroxyprogesterone caproate: A comparison with ritodrine  Antti Kauppila, Anna-Liisa Hartikainen-Sorri, Olli Jänne, Risto Tuimala, and Pentti A. Järvinen Oulu, Finland  Pregnancy and systemic lupus erythematosus	399
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida  Obstetrics  Blind oxytocin challenge test and perinatal outcome  K. J. Staisch, M.D., J. R. Westlake, Ph.D., and R. A. Bashore, M.D. Los Angeles, California  Suppression of threatened premature labor by administration of cortisol and 17α-hydroxyprogesterone caproate: A comparison with ritodrine  Antti Kauppila, Anna-Liisa Hartikainen-Sorri, Olli Jänne, Risto Tuimala, and Pentti A. Järvinen Oulu, Finland  Pregnancy and systemic lupus erythematosus  Mark T. Houser, M.D., Alfred J. Fish, M.D., George E. Tagatz, M.D.,	399
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida  Obstetrics  Blind oxytocin challenge test and perinatal outcome  K. J. Staisch, M.D., J. R. Westlake, Ph.D., and R. A. Bashore, M.D. Los Angeles, California  Suppression of threatened premature labor by administration of cortisol and 17α-hydroxyprogesterone caproate: A comparison with ritodrine  Antti Kauppila, Anna-Liisa Hartikainen-Sorri, Olli Jänne, Risto Tuimala, and Pentti A. Järvinen Oulu, Finland  Pregnancy and systemic lupus erythematosus  Mark T. Houser, M.D., Alfred J. Fish, M.D., George E. Tagatz, M.D., Preston P. Williams, M.D., and Alfred F. Michael, M.D.	399
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida  Obstetrics  Blind oxytocin challenge test and perinatal outcome  K. J. Staisch, M.D., J. R. Westlake, Ph.D., and R. A. Bashore, M.D. Los Angeles, California  Suppression of threatened premature labor by administration of cortisol and 17α-hydroxyprogesterone caproate: A comparison with ritodrine  Antti Kauppila, Anna-Liisa Hartikainen-Sorri, Olli Jänne, Risto Tuimala, and Pentti A. Järvinen Oulu, Finland  Pregnancy and systemic lupus erythematosus  Mark T. Houser, M.D., Alfred J. Fish, M.D., George E. Tagatz, M.D.,	399
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida  Obstetrics  Blind oxytocin challenge test and perinatal outcome  K. J. Staisch, M.D., J. R. Westlake, Ph.D., and R. A. Bashore, M.D. Los Angeles, California  Suppression of threatened premature labor by administration of cortisol and 17α-hydroxyprogesterone caproate: A comparison with ritodrine  Antti Kauppila, Anna-Liisa Hartikainen-Sorri, Olli Jänne, Risto Tuimala, and Pentti A. Järvinen Oulu, Finland  Pregnancy and systemic lupus erythematosus  Mark T. Houser, M.D., Alfred J. Fish, M.D., George E. Tagatz, M.D., Preston P. Williams, M.D., and Alfred F. Michael, M.D.  Minneapolis, Minnesota	399
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida  Obstetrics  Blind oxytocin challenge test and perinatal outcome  K. J. Staisch, M.D., J. R. Westlake, Ph.D., and R. A. Bashore, M.D. Los Angeles, California  Suppression of threatened premature labor by administration of cortisol and 17α-hydroxyprogesterone caproate: A comparison with ritodrine  Antti Kauppila, Anna-Liisa Hartikainen-Sorri, Olli Jänne, Risto Tuimala, and Pentti A. Järvinen Oulu, Finland  Pregnancy and systemic lupus erythematosus  Mark T. Houser, M.D., Alfred J. Fish, M.D., George E. Tagatz, M.D., Preston P. Williams, M.D., and Alfred F. Michael, M.D.  Minneapolis, Minnesota  Uterine and ovarian artery blood flow in the rhesus monkey near term	399 404 409
B. Frederick Helmkamp, M.D., Hans-B. Krebs, M.D., Michael B. Isikoff, M.D., Steven R. Poliakoff, M.D., and Hervy E. Averette, M.D. Miami, Florida  Obstetrics  Blind oxytocin challenge test and perinatal outcome  K. J. Staisch, M.D., J. R. Westlake, Ph.D., and R. A. Bashore, M.D. Los Angeles, California  Suppression of threatened premature labor by administration of cortisol and 17α-hydroxyprogesterone caproate: A comparison with ritodrine  Antti Kauppila, Anna-Liisa Hartikainen-Sorri, Olli Jänne, Risto Tuimala, and Pentti A. Järvinen Oulu, Finland  Pregnancy and systemic lupus erythematosus  Mark T. Houser, M.D., Alfred J. Fish, M.D., George E. Tagatz, M.D., Preston P. Williams, M.D., and Alfred F. Michael, M.D.  Minneapolis, Minnesota	399 404 409

(Contents continued on page 9)

# Just tell us where you want to live.

Hospital Corporation of America assists hundreds of physicians in locating solid practice opportunities each year. With HCA, you can choose a community that fits your lifestyle and know that the local hospital's staff and facilities will reflect your own high professional standards.

HCA owns or manages over 150 hospitals from San Francisco to Virginia...from Boston to Miami. Each hospital is well equipped, and professionally accredited and staffed. Practice opportunities are available in solo, groups, asso-

ciations and partnerships.

Contact HCA today. Let our free, no obligation Professional Relations Program match your needs with an HCA practice opportunity. Just send your curriculum vitae, with information on your personal, professional, and geographic interests, to: Charles M. Wooden, Director, Professional Relations, Hospital Corporation of America, One Park Plaza, Nashville, TN 37203. Telephone toll free 1-800-251-2561 or call collect (615) 327-9551.



Hospital Corporation of America.



## PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in these specially designed library file cases. Designed to keep your journal copies near at hand in your office, library, or home.

Your case is heavy bookbinder's board in a rich red Kivar cover. Files are scuff-resistant and washable.

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding.

Files are reasonably priced—only \$4.95 each, postpaid (3 for \$14., 6 for \$24.). Add \$1.00 postage per case for orders outside U. S. Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

Jesse Jones Box Corporation (est. 1843)
P. O. Box 5120
Philadelphia, Pa. 19141
Please send me, postpaid library cases for AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY at \$4.95 each (3/\$14., 6/\$24.)
<ul> <li>□ NEW SIZE (8½" × 11") 3 cases/year</li> <li>□ OLD SIZE (7½" × 10½") copies prior to 1975</li> </ul>
(2 cases/year)
Name
Address
City State 7:

## Contents continued from page 7

Maternofetal electrical potential difference in conscious sheep: Effect of fetal death	422
or acidosis  A. P. Weedon, T. E. Stacey, Jane F. Canning, R. H. T. Ward, and R. D. H. Boyd	
London, England	
Fetus, placenta, and newborn	
Nonstressed antepartum heart rate monitoring: Implications of decelerations after spontaneous contractions	429
G. H. A. Visser, C. W. G. Redman, H. J. Huisjes, and A. C. Turnbull	
Oxford, England, and Groningen, The Netherlands	
14 15 PM CONTRACTOR OF THE CON	436
First-trimester fetal chromosomal diagnosis using endocervical lavage: A negative evaluation	400
Marshall F. Goldberg, M.D., M.P.H., Andrew T. L. Chen, Ph.D., Young W. Ahn, M.D., and John A. Reidy, Ph.D.	
Atlanta, Georgia	444
Placental size during early pregnancy and fetal outcome: A preliminary report of a sequential ultrasonographic study	441
Henk J. Hoogland, M.D., Jelte de Haan, M.D., and Chester B. Martin, Jr., M.D.  Nijmegen, The Netherlands	
Mechanisms of beat-to-beat variability in the heart rate of the neonatal lamb. I.	444
Influence of the autonomic nervous system	
Marcelo Zugaib, Alan B. Forsythe, Bahij Nuwayhid, Stephen M. Lieb, Khalil Tabsh,	
Risto Erkkola, Etsuo Ushioda, C. R. Brinkman III, and N. S. Assali  Los Angeles, California	
Mechanisms of beat-to-beat variability in the heart rate of the neonatal lamb. II.  Effects of hypoxia	453
Marcelo Zugaib, Alan B. Forsythe, Bahij Nuwayhid, Stephen M. Lieb, Khalil Tabsh, Risto	
Erkkola, Etsuo Ushioda, S. Murad, C. R. Brinkman III. and N. S. Assali  Los Angeles, California	
Communications in brief	
Effect of in utero intravenous administration of thyroxine and other hormones on	459
the lung fluid lecithin/sphingomyelin ratio in the fetal lamb	
Uchenna C. Nwosu, M.D., Endla K. Anday, M.D., Ronald J. Bolognese, M.D.,	
Alfred M. Bongiovanni, M.D., and Maria Delivoria-Papadopoulos, M.D.  Philadelphia, Pennsylvania	
L-5 Radiculopathy secondary to a uterine leiomyoma in a primigravid patient	460
L. P. M. Heffernan, M.D., F.R.C.P.(C.), R. C. Fraser, M.D., F.R.C.S.(C.), and	
R. A. Purdy, M.D., F.R.C.P.(C.)	
Halifax, Nova Scotia, Canada	
(Contents continued o	n page 11

## LOUISIANA STATE UNIVERSITY IN NEW ORLEANS

Following full-time faculty positions are available:

- ▼. Director of Gynecologic Endocrinology
- 2. Director of Gynecologic Oncology
- 3. Director of Maternal-Fetal Medicine
- 4. General Obstetrician-Gynecologist
- 5. Director of program at affiliated Charity Hospital, Baton Rouge, La.

Interested applicants should send a curriculum vitae to:

Charles A. White, M.D.
Professor and Head
Department of Obstetrics and Gynecology
L.S.U School of Medicine
1542 Tulane Avenue
New Orleans, Louisiana 70112

An Affirmative Action/Equal Opportunity Employer

## Permanente

PC/PHYSICIANS & SURGEONS

## GROUP PRACTICE OPPORTUNITIES Pacific Northwest

Rapid membership growth has created an immediate opening in the Department of Obstetrics/Gynecology of Northwest Permanente, P.C. in Portland, Oregon. We are seeking obstetrician/gynecologists to join an active service with over 3,900 annual deliveries, a high risk intensive care nursery and complete fetal monitoring equipment.

Nortwhest Permanente, P.C. is a professional medical corporation which provides health care services to the 235,000 members of the Kaiser Foundation Health Plan of Oregon. Through its association with Kaiser Foundation Health Plan, a federally qualified HMO, Northwest Permanente, P.C. operates nine outpatient clinics and two full service hospitals.

The medical practice is varied and professionally stimulating offering the physician a pure practice free of business and administrative concerns. A comprehensive salary and benefits package including a sabbatical program, malpractice coverage, three weeks vacation and one week educational leave to start, life, medical/dental and disability insurance along with two excellent retirement programs is provided. The physician is eligible for ownership participation after two years.

Portland, Oregon, on the Columbia and Willamette Rivers, is a city with a moderate climate located in a stable, prosperous economic region of the beautiful Northwest. Outdoor recreational facilities are superb and include excellent skiing, backpacking, fishing and boating opportunities. The Environmental Protection Agency, in a recent study, selected Portland as the "most livable city" in the United States.

Please send two (2) copies of a curriculum vitae with your initial response to Marvin P. Goldberg, M.D. President, Northwest Permanente, P.C., 1500 S.W. 1st Avenue, 11th Floor, Portland, Oregon, 97201.

## NORTHWEST PERMANENTE, P.C. — PHYSICIANS & SURGEONS

An Equal Opportunity Employer

## CLINICAL BIOSTATISTICS:

## here's why you'll benefit from this book

- authoritative articles from <u>Clinical Pharmacology and</u> <u>Therapeutics</u>
- clear and easy-to-read explanations of essential statistical concepts
- provocative insights into the common sense and science behind statistical data

## CLINICAL BIOSTATISTICS

This unique book critically examines the entire field of clinical biostatistics. It presents a series of original articles that first appeared over a five year period in *Clinical Pharmacology and Therapeutics*. Widespread reader acclaim and the timeliness of the subject prompted publication of the essays into convenient book form.

The essays are logically arranged into 29 chapters and organized into five major sections, each preceded by brief commentary written especially for the book. You'll find informative discussions on the diverse statistical techniques used in medical practice and research; research and design problems; presentation of data; and methods of data analysis. Dr. Feinstein has reorganized his original articles to provide you with a completely current guide to the biostatistics used in both clinical and investigative situations. He also offers valuable insights into topics either totally neglected or inadequately covered in conventional texts. Throughout, discussions are written in lively prose style, which makes the subject both interesting to read and easy-to-understand. Why not benefit from Dr. Feinstein's expert guidance firsthand—order your copy of CLINICAL BIOSTATISTICS today!

By **Alvan R. Feinstein**, M.D., 1977, 468 pages plus FM I-XIV, 6-7/8" x 10", 10 illustrations. Price, \$21.50

## ORDER BY PHONE!

Call toll free (800) 325-4177 ext. 10. In Missouri call collect—(314) 872-8370 ext. 10 during normal business hours. A80794

Price effective in U.S.A. only.



THE C. V. MOSBY COMPANY 11830 WESTLINE INDUSTRIAL DRIVE ST. LOUIS, MISSOURI 63141

## Contents continued from page 9

Fluorescein angiography in hypertensive pregnancies	461
B. Donkers and D. Jansonius	
Deventer, The Netherlands	
The "female echo": Prenatal determination of the female fetus by ultrasound	463
Annemarie Schotten and Christa Giese  Aachen, West Germany	
Auchen, west Germany	101
Ultrasonographic diagnosis of fetal cystic hygroma	464
William F. O'Brien, Lieutenant Commander, MC, USNR, Robert C. Cefalo, M.D., Ph.D., and	
Donald G. Bair, Lieutenant, MC, USNR	
Bethesda, Maryland	
The effect of maternal dietary fat on fetal pulmonary maturation in rats	466
George H. Nelson, M.D., Ph.D., James McPherson, Jr, M.D., Lance Perling, B.S., and	
Rick Ciechan, B.S.  Augusta, Georgia	
선생님들이 가는 사람들이 가는 사람들이 되었다면 그렇게 되었다. 그런 그렇게 되는 것이 되고 있다면 하는데 되었다면 하는데 되었다.	407
Serial ultrasonographic biparietal diameters for prediction of estimated date of	467
confinement	1
William F. O'Brien, Lieutenant Commander, MC, USNR, Charles C. Coddington, Lieutenant, MC,	
USN, and Robert C. Cefalo, M.D., Ph.D., F.A.C.O.G.	
Bethesda, Maryland, and Chapel Hill, North Carolina	
Multiple pulmonary fibroleiomyomas	468
Luke G. Tedeschi, M.D.	
Framingham and Boston, Massachusetts	
Trumingham una Boston, Massachusens	
Correspondence	
Correspondence	471
Books	
	A STATE OF THE STA
Books received	474
Erratum	
Occupation of orticle by Denowitz and Wenzel, entitled "Endometritis following	473
Correction of article by Donowitz and Wenzel, entitled "Endometritis following cesarean section"	
cesarean section	

Information for authors on page 21
Index to advertisers on page 39



## convenience of Gantanol

sulfamethoxazole/Roche



Convenient, economical first-line therapy

Gantanol 05

sulfamethoxazole/Roche 2 tablets initially, then only 1 tablet B.I.D.

## Only one tablet B.I.D.

Only Gantanol DS offers the convenience of a *single* sulfonamide tablet on a *b.i.d.* schedule. With fewer daily doses, patients are more likely to comply with your prescribed regimen.

## Effective first-line therapy

In a controlled study of 406 patients involving *E. coli* and the other most common causative organisms of acute nonobstructed cystitis, nearly 9 out of 10 patients achieved clear cultures with Gantanol. (Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.)

Gantanol is contraindicated in sulfonamide hypersensitivity, pregnancy, lactation, and infants under two months of age. During therapy instruct patients to maintain adequate fluid intake; perform frequent CBC's and urinalyses with careful microscopic examination.

## **Economical**

Gantanol therapy, which often costs less than other frequently prescribed urinary antibacterials, becomes even more economical for your patients when you select Gantanol DS (double strength) tablets.



**Gantanol**°

sulfamethoxazole/Roche

4 tablets initially, then only 2 tablets B.I.D.

## Only 1 tablet B.I.D.

## Gantanol® DS sulfamethoxazole/Roche

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Acute, recurrent or chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually E. coli, Klebsiella-Aerobacter, staphylococcus, Proteus mirabilis and, less frequently, Proteus vulgaris), in the absence of obstructive uropathy or foreign bodies. Note: Carefully coordinate in vitro sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections. Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level

Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

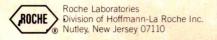
Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: Blood dyscrasias (agranulocytosis, aplastic anemia, thrombocytopenia leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); allergic reactions (erythema multiforme, skin eruptions epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); gastrointestinal reactions (nausea emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); CNS reactions (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); miscellaneous reactions (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypo-glycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis). Usual adult dosage: 2 Gm (2 DS tabs or 4 tabs or 4' teasp.) initially, then 1 Gm b.i.d. or t.i.d. depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs b.i.d. Maximum dose should not exceed 75 mg/kg/24 hrs.

Supplied: DS (double strength) Tablets, 1 Gm sulfamethoxazole; Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazole/teaspoonful.



## EDITORS! REVIEWERS! AUTHORS!

For you . . . a new book that contains virtually everything you want to know about

## THE SCIENTIFIC JOURNAL: EDITORIAL POLICIES AND PRACTICES

## Guidelines for Editors, Reviewers, and Authors

In 1665 the first scholarly journal was published in France. Since that time, there has been no one source of editorial guidelines for journal editors. This new book now provides you with such a source.

## YOU DECIDE YOUR OWN APPROACH!

Presenting the advantages and disadvantages of each specific decision, eminent editors offer you various recommendations, discussions, and opinions concerning the problems you may encounter:

"Because we are aware that there is no 'right' policy on most editorial matters, we have tried not to prescribe rules, but have, instead, explored various facets of the problems that confront the editor in his daily work."

The book is divided into two general sections: editorial policies, which usually require major decisions; and editorial practices, which involve minor decisions, often about format or mechanical style. You'll find essays exploring: the manuscript reviewing system; special types of manuscripts (abstracts, transactions, solicited manuscripts, book reviews). You'll value chapters which cover: information for authors; copyright; errata; references cited; copy-editing; journal cover; etc.

From "the purpose of scientific journals" to "binding practices," this new book contains virtually everything you want to know as editor, reviewer, or author. See for yourself!

By Lois DeBakey, Ph.D. In collaboration with: Paul F. Cranefield, M.D., Ph.D.; Ayodhya P. Gupta, M.D.; Franz J. Ingelfinger, M.D.; Robert J. Levine, M.D.; Robert H. Moser, M.D.; J. Roger Porter, Ph.D.; and F. Peter Woodford, Ph.D. August, 1976. 128 pages, 6" × 9". Price, \$12.50.

Please send me on 30-day approval THE SCIENTIFIC JOURNAL: EDITORIAL POLICIES AND PRACTICES.
Price, \$12.50.
☐ Bill me ☐ Master Charge #
□ Payment enclosed
Name
Address
City
StateZip Code
MOSBY
TIMES MIRROR

30-day approval offer good only in continental U.S. and Canada.
A60519

THE C. V. MOSBY COMPANY

11830 WESTLINE INDUSTRIAL DRIVE
ST. LOUIS, MISSOURI 63141

## American Journal of Obstetrics and Gynecology

## **Editors**

JOHN I. BREWER, Editor in Chief

FREDERICK P. ZUSPAN, E. J. QUILLIGAN, Editors

ALBERT B. GERBIE, Associate Editor

HOWARD C. TAYLOR, JR., ALLAN C. BARNES, Emeritus Editors

## Advisory committee on policy

C. D. Christian

Leo J. Dunn

David Figge

Fred T. Given

A. Brian Little

Edgar L. Makowski

George D. Malkasian

Roy T. Parker

W. Ann Reynolds

J. C. G. Whetham

## Board of corresponding editors

Oscar Aguero, Caracas Frederick Kubli, Heidelberg Pierre O. Hubinont, Brussels Malcolm Symonds, Nottingham Ichiro Taki, Fukuoka

## HER OCISIT FOR BETTER OR WORSE.

If it's NORLESTRIN® 1/50 (I mg norethindrone acetate and 50 mcg ethinyl estradiol tablets, USP), it's exactly what she expects...and it's exactly what you've come to expect in terms of efficacy and patient acceptance. Ever since NORLESTRIN 1/50 was first introduced over a decade ago, it has performed as promised, consistently providing what patients and their physicians want from an OC: virtually complete control of conception plus relative freedom from annoying side effects like breakthrough bleeding.

With its combination of ethinyl estradiol and norethindrone acetate, NORLESTRIN 1/50 gives patients the comfort and confidence they look for in an OC. Cycle after cycle, NORLESTRIN 1/50 gives your patient no more estrogen than she needs.

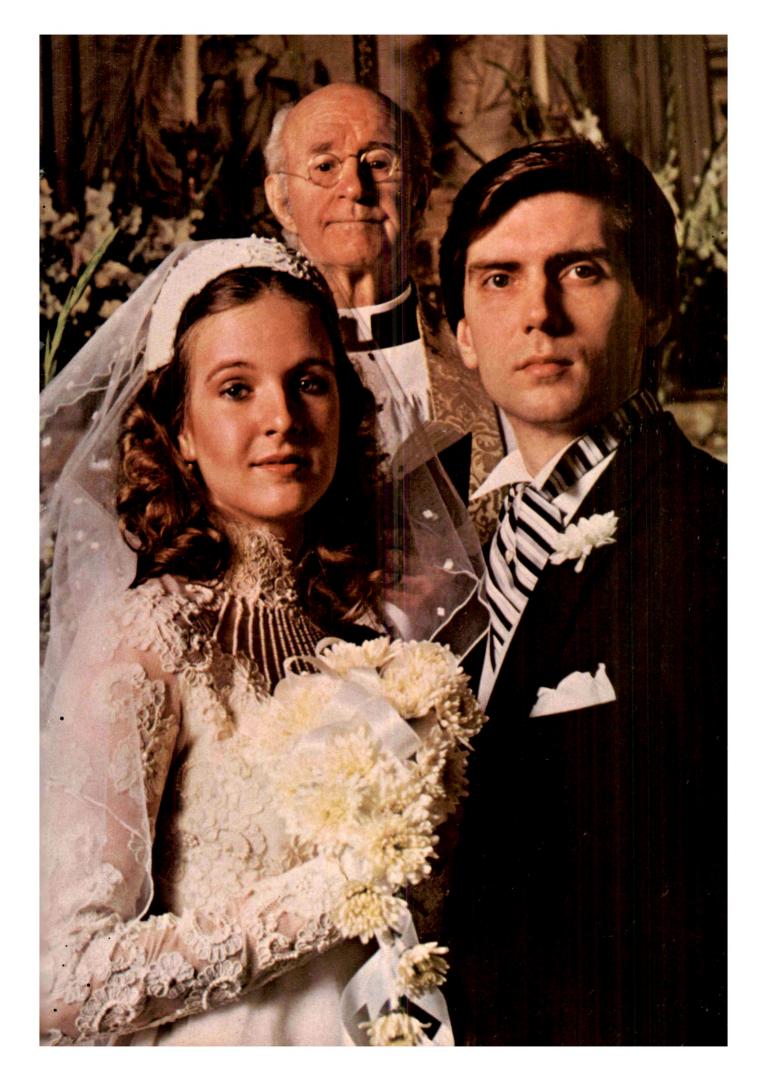
## NORLESTRIN®

(1 mg norethindrone acetate and 50 mcg ethinyl estradiol tablets, USP)

YOU COULDN'T DO BETTER.

PARKE-DAVIS

Please see following page for brief summary of prescribing information.



## Brief Summary of Prescribing Information.

diol tablets, USP) See section under Special Notes on Administration and HOW SUPPLIED.

Each yellow tablet contains: norethindrone acetate (17 alpha-ethinyl-19-nortestosterone acetate), 1 mg; ethinyl estradiol (17 alpha-ethinyl-1,3,5(10)-estratriene-3, 17 beta-diol), 50

### DESCRIPTION

Norlestrin 1/50 Products are progestogen-estrogen combinations.

INDICATIONS AND USAGE

Norlestrin 1/50 Products are indicated for the prevention of pregnancy in women who elect

to use oral contraceptives as a method of contraception.
In clinical trials with Norlestrin 1/50 involving 25,983 therapy cycles, there was a pregnancy rate of 0.05 per 100 women years.

Dose-related risk of thromboembolism from oral contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with cy rate and patient acceptance.

CONTRAINDICATIONS

Thrombophlebitis or thromboembolic disorders
A past history of deep-vein thrombophlebitis or thromboembolic disorders

2. A past history of deep-vein informbonheolits of informbon as Cerebral vascular or coronary artery disease 4. Known or suspected carcinoma of the breast 5. Known or suspected estrogen-dependent neoplasia 6. Undiagnosed abnormal genital bleeding 7. Known or suspected pregnancy (See WARNING No. 5.)

### WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious additional polarities because of the production of the product

conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these

1. Thromboembolic Disorders and Other Vascular Problems: An increased risk of throm

1. Thromboembolic Disorders and Other Vascular Problems: An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established. Studies have demonstrated an increased risk of fatal and nontatal venous thromboembolism and stroke, both hemorrhagic and thrombotic.

Cerebrovascular disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater.

Myocardial infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association. These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesteroleemia, obesity, diabetes, history of preclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor.

coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor.

If has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke. The amount of smoking is also an important factor.

Risk of dose: In an analysis of data, British investigators conflued that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives; however, the quantity of estrogen may not be the sole factor involved.

Estimate of excess mortality from circulatory diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers.

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke.

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preclampto toxemia, and especially by cigarette smoking.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombolic disorders. Should any occur or be suspected, the drug should be discontinued immediately.

A fourfold to sixfold increased risk of postsurgery thromboembolic compl

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization

prolonged immobilization.

2. Ocular lesions: Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions.

3. Carcinoma: Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver.

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported. However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combinating or propertingen-only oral contraceptives.

combination or progestogen-only oral contraceptives.

Studies found no evidence of increase in breast cancer in women taking oral contraceptives; however, an excess risk in users with documented benign breast disease was

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of users is, nevertheless, essential. In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms.

breast cancer, of who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care.

4. Hepatic Tumors: Benign hepatic adenomas have been found to be associated with oral contraceptives. Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. Usage in or Immediately Preceding Pregnancy; Birth Defects in Offspring, and Malignancy in Female Offspring: During early pregnancy, female sex hormones may seriously damage the offspring.

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy.

been reported with the use of oral contraceptives in pregnancy.

There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives.

Pregnancy should be ruled out before continuing an oral contraceptive in any patient whe has missed two consecutive menstrual periods. If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed.

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive.

Administration of progetogen-pally or progetogen-strongen compinations to induce

use an alternate form of contraception for a period of time before attempting to conceive. Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. Gallbladder Disease: Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives.

7. Carbohydrate and Lipid Metabolic Effects. Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed.

8. Elevated Blood Pressure: An increase in blood pressure has been reported in patients receiving oral contraceptives. The prevalence in users increases with longer exposure. Age is also strongly correlated with development of hypertension. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure.

Headache: Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contracep-

tives.

10. Bleeding Irregularities: Breakthrough bleeding, spotting, and amenorrhea are frequen reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, nonfunctional causes should be borne in mind. In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives.

11. Ectopic Pregnancy: Ectopic as well as intrauterine pregnancy may occur in contraceptive failure.

12. Breast Feeding: Oral contraceptives may interfere with lactation. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs.

PRECAUTIONS

PRECAUTIONS

1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.

2. Preexisting uterine leiomyomata may increase in size.

3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious depres.

A cateline with a history of psychic depression should be darefully observed and the discontinued if depression recurs to a serious degree.

4. Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice. If jaundice develops, the medication should be discontinued.

6. Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function.

7. Users may have disturbances in normal tryptophan metabolism, which may result in a

relative pyridoxine deficiency.
8. Serum folate levels may be depressed.
9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted.

10. Certain endocrine and liver function tests and blood components may be affected (a) increased sulfobromophthalein retention. (b) increased prothrombin and factors VII.

VIII., IX, and X; decreased antithrombin 3: increased norepinephrine-induced platelet
aggregability. (c) Increased thyroid-binding globulin (TBG) leading to increased circulating
total thyroid hormone. (d) Decreased pregnanediol excretion. (e) Reduced response to

Drug interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin and an association has been ith barbiturates, phenylbutazone, phenytoin sodium, and ampicillin.

### ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with oral contraceptives: thrombophlebitis; pulmonary embolism; coronary thrombosis; cerebral thrombosis; cerebral hemorrhage; hypertension; gallbladder disease; benign hepatomas;

contraceptives: thrombophiotist; pulmonary embolism; coronary Informbosis; cerebral hemorrhage; hypertension; gallbladder disease; benign hepatomas; congenital anomalies.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, eg, retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: gastrointestinal symptoms; breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma; breast changes; change in weight; change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately post partum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature; intolerance to contact lenses.

The following adverse reactions have been reported and the association has been neither confirmed nor refuted; premenstrual-like syndrome; cataracts; changes in libido; chorea; changes in appetite; cystitis-like syndrome; headache; nervousness; dizziness; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis porphyria.

### Special Notes on Administration

Special Notes on Administration
Norlestrin [Eq 1/50 (norethindrone acetate and ethinyl estradiol tablets, USP) and Norlestrin
[28] 1/50 — Menstruation usually begins two or three days, but may begin as late as the fourth
or fifth day, after the brown ferrous fumarate or white inert tablets have been started.
Norlestrin[27]1/50 — Menstruation usually begins two or three days, but may begin as late
as the fourth or fifth day, after discontinuing medication.
After several months on treatment, bleeding may be reduced to a point of virtual absence,
reduced flow may be a result of medication and not indicative of pregnancy.
HOW SUPPLIED

### HOW SUPPLIED

HOW SUPPLIED

Norlestrin [F2] 1/50 is available in minicompacts each containing 21 yellow tablets and 7 brown tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous furmarate. Available in packages of five minicompacts and packages of five refills.

Norlestrin [28] 1/50 is available in minicompacts each containing 21 yellow tablets and 7 white inert tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five minicompacts and in packages of five refills.

Norlestrin [21] 1/50 is available in minicompacts each containing 21 yellow tablets. Each yellow tablet contains 1 mg of norethindrone acetate and 50 mcg of ethinyl estradiol. Available in packages of five minicompacts and packages of five refills.

PARKE-DAVIS Div of Warner-Lambert Co Morris Plains, NJ 07950 USA

PD-JA-0270-1-P (3-80)

## American Journal of Obstetrics and Gynecology

in addition to those listed on the front cover the Journal is the official publication of the following societies

NEW YORK OBSTETRICAL SOCIETY OBSTETRICAL SOCIETY OF PHILADELPHIA BROOKLYN GYNECOLOGICAL SOCIETY ST. LOUIS GYNECOLOGICAL SOCIETY NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY THE OBSTETRICAL AND GYNECOLOGICAL SOCIETY OF MARYLAND CHICAGO GYNECOLOGICAL SOCIETY CINCINNATI OBSTETRICAL AND GYNECOLOGICAL SOCIETY WASHINGTON GYNECOLOGICAL SOCIETY PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY BOSTON OBSTETRICAL SOCIETY LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY SEATTLE GYNECOLOGICAL SOCIETY ALABAMA ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS AKRON OBSTETRICAL AND GYNECOLOGICAL SOCIETY KANSAS CITY GYNECOLOGICAL SOCIETY CENTRAL NEW YORK ASSOCIATION OF GYNECOLOGISTS AND OBSTETRICIANS

NEW JERSEY OBSTETRICAL AND GYNECOLOGICAL SOCIETY IOWA OBSTETRIC AND GYNECOLOGIC SOCIETY THE TEXAS ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS OKLAHOMA CITY OBSTETRICAL AND GYNECOLOGICAL SOCIETY MEMPHIS OBSTETRICAL AND GYNECOLOGICAL SOCIETY UTAH OBSTETRICAL AND GYNECOLOGICAL SOCIETY ROCHESTER OBSTETRICAL AND GYNECOLOGICAL SOCIETY ARKANSAS OBSTETRICAL AND GYNECOLOGICAL SOCIETY TENNESSEE STATE OBSTETRICAL AND GYNECOLOGICAL SOCIETY NEW YORK GYNECOLOGICAL SOCIETY PACIFIC NORTHWEST OESTETRICAL AND GYNECOLOGICAL ASSOCIATION BUFFALO OBSTETRICAL AND GYNECOLOGICAL SOCIETY SAN FRANCISCO GYNECOLOGICAL SOCIETY JACKSON GYNECIC SOCIETY INDIANA OBSTETRICAL AND GYNECOLOGICAL SOCIETY THE MINNESOTA OBSTETRICAL AND GYNECOLOGICAL SOCIETY

## TEACHING HOSPITAL KING FAISAL UNIVERSITY COLLEGE OF MEDICINE SAUDI ARABIA

The new 380-bed AlKhobar Teaching Hospital, affiliated with King Faisal University College of Medicine, Eastern Province, Saudi Arabia, invites applications from board certified clinicians in:

### OBSTETRICS AND GYNECOLOGY

SALARIES highly competitive and negotiable. Instruction is in English. Interviews scheduled during late-1980 and early-1981.

CONTRACTS are for one year and renewable. Clinicians hold fac-

ulty appointments.

BENEFITS include free furnished housing, airtickets to and from Saudi Arabia one time each year for a family of four, 60-day vacation with pay, generous overweight and educational allowances. No Saudi income tax.

Please send curriculum vitae with current telephone numbers, and the names and addresses of three references to:

OR

Dr. Tawfiq Tamimi, Dean

College of Medicine, King Faisal University

c/o Saudi Arabian

P.O. Box 2

**Educational Mission** 

Sunbury-on-Thames

2425 West Loop South

Middlesex TW16 5JP

Houston, TX 77027

England

## MATERNAL-FETAL FFLIOW

Approved Fellowship offered in a University hospital in New Jersey. Extensive basic science research facilities and required graduate courses are integrated with clinical responsibilities in high risk obstetrics to fulfill Board requirements. Referral patterns are established through a well developed maternal transport system. Contact John T. Harrigan, M.D., Professor and Director of the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology.



COLLEGE OF MEDICINE
AND DENTISTRY OF NEW JERSEY
Rutgers Medical School
P.O. Box 101, Piscataway, NJ 08854

Equal Opportunity/Affirmative Action Employer

Multi-Specialty Group Practice Northeast

The Capital Area Community Health Plan, a Federally Qualified Health Maintenance Organization, is seeking two Board Eligible or certified Obstetricians/Gynecologists. The individual who accepts this position will join a medical staff which includes the subspecialties of Dentistry, Family Care, Internal Medicine, Pediatrics, Psychiatry, Otolaryngology, Radiology, Surgery and others.

CHP is located in New York's Capital District, an educational center within easy reach of Boston, New York City, Montreal, etc., which has an abundance of cultural and recreational options and offers a wide range of residential styles.

Professionals enjoy attractive salary and fringe benefits.

Inquiries about our practice should be addressed to STANLEY E. KILTY, M.D., Medical Director, CHP, 1201 Troy-Schenectady Road, Latham, New York 12110. Collect telephone inquiries are welcome: 518-783-3110.



## Position Available

Board Certified or Board Eligible Maternal/Fetal Medicine Specialist for Affiliated Teaching Unit of the University of North Carolina at Chapel Hill. Regional Referral Center with a full residency program located in Wilmington, North Carolina. Full-time, tenure track appointment. Rank and salary negotiable depending on previous experience. All fully qualified applicants are welcome regardless of sex and race. The University of North Carolina at Chapel Hill is an AFFIRMATIVE ACTION/EQUAL OPPORTUNITY EMPLOYER. Applicants should send curriculum vitae to:

Robert C. Cefalo, M.D., Ph.D.
Acting Chairman
Director, Maternal/Fetal Medicine Division
Department of Obstetrics & Gynecology
University of North Carolina
School of Medicine
4019 Old Clinic Building
Chapel Hill, N.C. 27514

## American Journal of Obstetrics and Gynecology

Copyright © 1980 by The C. V. Mosby Company

Editors

John I. Brewer, Editor in Chief 710 North Fairbanks Court, Chicago, Illinois 60611

## Frederick P. Zuspan, Editor

The Ohio State University, 410 W. 10th Ave., Columbus, Ohio 43210

### Information for authors

Submission of contributions. Manuscripts should in general be sent to a particular Editor according to the following plan: If it is from the southeastern quadrant of the United States or from Canada, or if it has been presented before one of the official sponsoring societies, to Dr. Brewer; if from the northeastern quadrant (including Ohio), or if it is a Clinical Opinion or a Letter to the Editors, to Dr. Zuspan; if from the north central states, any of the United States west of the Mississippi, Hawaii, Alaska, or abroad, to Dr. Quilligan.

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following written statement, signed by one author: "The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C. V. Mosby Company in the event the work is published. The undersigned author warrants that the article is original, is not under consideration by another journal, and has not been previously published. I sign for and accept responsibility for releasing this material on behalf of any and all co-authors." Authors will be consulted, when possible, regarding republication of their material.

All articles published in this JOURNAL must be contributed to it exclusively. Articles previously published in another language are not acceptable.

It is assumed by the Editors that articles emanating from a particular institution are submitted with the approval of the requisite authority.

Articles dealing with human experimentation cannot be accepted unless the experiment was approved by the author's local Human Experimentation Committee.

Statements and opinions expressed in the articles and communications herein are those of the author(s) and not necessarily those of the Editor(s) or Publisher and the Editor(s) and Publisher disclaim any responsibility or liability for such material. Neither the Editor(s) nor the Publisher guarantee, warrant, or endorse any product or service advertised in this publication, nor do they guarantee any claim made by the manufacturer of such product or service.

Manuscripts. Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. The original and one copy of the manuscript are required. References should be placed at the end of the article. They should include name of author(s), article title, name of periodical, volume, page, and year. Name of periodical should conform to that shown in latest List of Journals Indexed in Index Medicus. For reference style see current issue of JOURNAL. Authors are encouraged to limit references to 16, except for Communications in Brief, limited to 2, Current Investigation and Clinical Opinion, limited to 6, and Current Developments, for which there is no limit. Illustrations accompanying manuscripts should be numbered, provided with suitable

## E. J. Quilligan, Editor

University of California, Irvine, Medical Center, Department of Obstetrics and Gynecology, Building 16, 101 City Dr. S., Orange, California 92668

Albert B. Gerbie, Associate Editor
710 North Fairbanks Court, Chicago, Illinois 60611

legends, and marked lightly on the back with the author's name. Authors should indicate on the manuscript the approximate position of tables and text figures.

Tables should be typed on separate sheets of paper, not in the text, with one table to a page. They should be numbered in sequence and each must be referred to at an appropriate point in the text. Captions of the tables should be brief, yet indicate clearly the purpose or content of each table. Rows and columns in the table should precisely define the nature of the data in each. Abbreviations in tables should be used as little as possible and if abbreviations are used they should be explained in a footnote to the table.

An abstract of 50 to 150 words, to be published as an introduction, should accompany each manuscript and should be typed on a separate sheet of paper.

A footnote should be included which gives the name and complete mailing address of the person to whom reprint requests and correspondence should be sent.

A Guide to Writing for the American Journal of Obstetrics and Gynecology may be obtained from the Publisher on request.

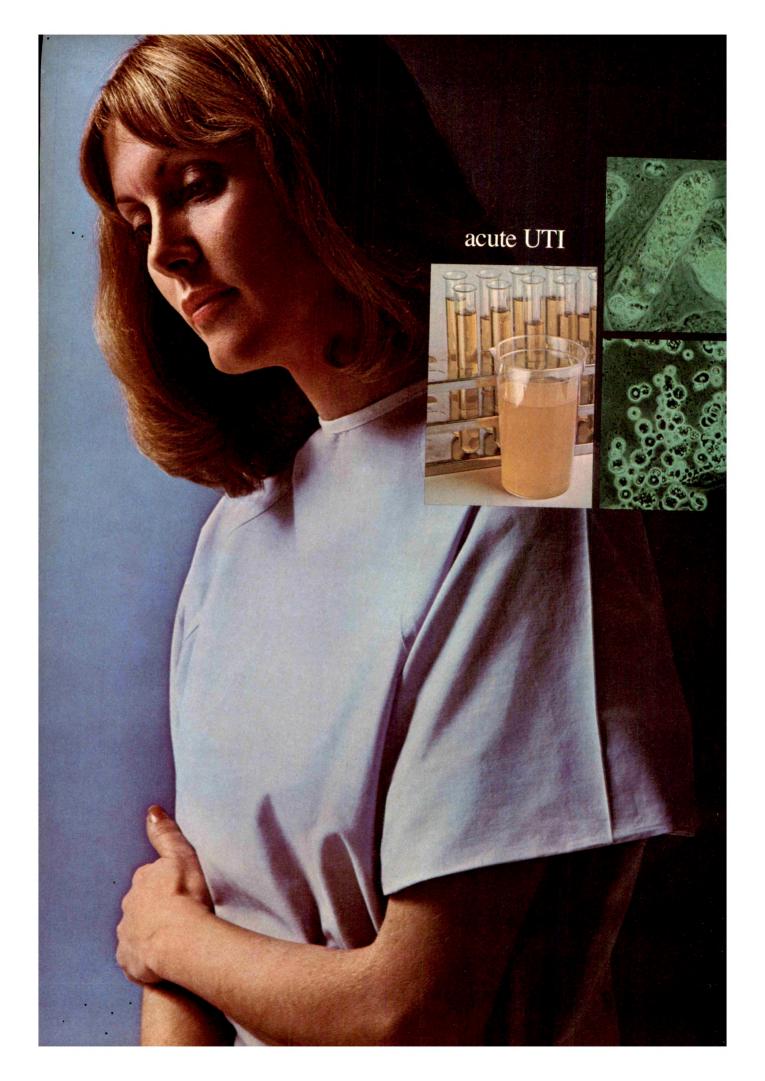
Illustrations. A reasonable number of halftone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the Editors for color plates, elaborate tables, or extra illustrations. Original drawings or graphs should be drawn with black India ink. Typewritten or freehand lettering is not acceptable. All lettering must be done professionally. Do not send original art work, x-ray films, or ECG tracings. Glossy print photographs are preferred, for good black and white contrast is essential. Illustrations will be returned only if requested by the author.

Announcements. Announcements of meetings must be received by Dr. Brewer at least 2½ months prior to the time of the meeting. Such announcements should concern major meetings and other significant activities. Announcements of symposia or seminars for which fees are charged are not published in the scientific pages of the JOURNAL but may be submitted for paid advertisements, if desired.

Letters to the Editors. A brief Letter to the Editors commenting upon some article which has appeared in the JOURNAL will be considered for publication. The writer of the original article will have an opportunity to reply to unfavorable comments. A brief case presentation of special interest in the form of a Letter to the Editors will also be considered for publication. All such letters should be sent to Dr. Zuspan.

**Books.** Books received will be listed in the JOURNAL. They should be sent to Dr. Gerbie.

Reprints. Reprints of articles must be ordered from the Publishers, The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141, who will send their schedule of prices. Individual reprints of an article must be obtained through the author.

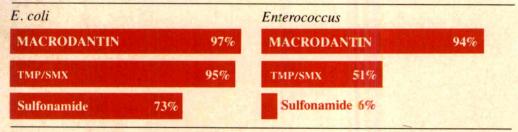


## In acute UTI

## When your first choice is Macrodantin<sup>®</sup> you'll rarely need a second one

Macrodantin is potent against both major uropathogens in office practice—E. coli, the most common, and enterococcus—unlike other widely prescribed antimicrobials used individually or in combination.

Superior in vitro\* against the two most common uropathogens'



- \*In vitro data do not necessarily predict clinical efficacy.
- 1. PMR Bacteriologic Report, Summer Series 1979:
- a national bacteriologic monitoring service for 200 acute-care hospitals of 100 beds or more.
- Macrodantin remains consistently effective year after year resistance is negligible
- Does not foster resistant bowel flora which may recycle infection.
- Does not change normal vaginal flora...little risk of Candida overgrowth.
- Concentrates its action in the urinary tract.

Lets you reserve systemic agents for systemic infection.

...too valuable to keep in reserve

## Macrodantin

(nitrofurantoin macrocrystals)

...too valuable to keep in reserve

## **Macrodantin**<sup>®</sup>

## (nitrofurantoin macrocrystals)

Capsules: 25,50,100mg

INDICATIONS: Macrodantin is indicated for the treatment of urinary tract infections when due to susceptible strains of *Eschericha coli*, enterococci, *Staphylococcus aureus* (it is not indicated for the treatment of associated renal cortical or perinephric abscesses), and certain susceptible strains of *Klebsiella* species, *Enterobacter* species, and *Proteus* species.

NOTE: Specimens for culture and susceptibility testing should be obtained prior to and during drug administration.

CONTRAINDICATIONS: Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 40 ml per minute) are contraindications to therapy with this drug. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of the drug. For the same reason, this drug is much less effective under these circumstances.

The drug is contraindicated in pregnant patients at term as well as in infants under one month of age because of the possibility of hemolytic anemia due to immature enzyme systems (glutathione instability).

The drug is also contraindicated in those patients with known hypersensitivity to Macrodantin, Furadantin® (nitrofurantoin), and other nitrofurantoin preparations.

WARNINGS: Acute, subacute and chronic pulmonary reactions have been observed in patients treated with nitrofurantoin products. If these reactions occur, the drug should be withdrawn and appropriate measures should be taken.

An insidious onset of pulmonary reactions (diffuse interstitial pneumonitis or pulmonary fibrosis, or both) in patients on long-term therapy warrants close monitoring of these patients.

There have been isolated reports giving pulmonary reactions as a contributing cause of death. (See Hypersensitivity reactions.)

Cases of hemolytic anemia of the primaquine sensitivity type have been induced by Macrodantin. The hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Negroes and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Any sign of hemolysis is an indication to discontinue the drug. Hemolysis ceases when the drug is with-

Pseudomonas is the organism most commonly implicated in superinfections in patients treated with Macrodantin.

Hepatitis, including chronic active hepatitis, has been observed rarely. Fatalities have been reported. The mechanism appears to be of an idiosyncratic hypersensitive type.

PRECAUTIONS: Peripheral neuropathy may occur with Macrodantin therapy; this may become severe or irreversible. Fatalities have been reported. Predisposing conditions such as renal impairment (creatinine clearance under 40 ml per minute), anemia, diabetes, electrolyte imbalance, vitamin B deficiency, and debilitating disease may enhance such occurrence.

Usage in Pregnancy: The safety of Macrodantin during pregnancy and lactation has not been established. Use of this drug in women of childbearing potential requires that the anticipated benefit be weighed against the possible risks.

ADVERSE REACTIONS: Gastrointestinal reactions: Anorexia, nausea and emesis are the most frequent reactions; abdominal pain and diarrhea occur less frequently. These dose-related toxicity reactions can be minimized by reduction of dosage, especially in the female patient. Hepatitis occurs rarely.

Hypersensitivity reactions: Pulmonary sensitivity reactions may occur, which can be acute, subacute, or chronic.

Acute reactions are commonly manifested by fever, chills, cough, chest pain, dyspnea, pulmonary infiltration with consolidation or pleural effusion on x-ray, and eosinophilia. The acute reactions usually occur within the first week of treatment and are reversible with cessation of therapy. Resolution may be dramatic.

In subacute reactions, fever and eosinophilia are observed less often. Recovery is somewhat slower, perhaps as long as several months. If the symptoms are not recognized as being drug related and nitrofurantoin is not withdrawn, symptoms may become more severe.

Chronic pulmonary reactions are more likely to occur in patients who have been on continuous nitrofurantoin therapy for six months or longer. The insidious onset of malaise, dyspnea or exertion, cough, and altered pulmonary function are common manifestations. Roentgenographic and histologic findings of diffuse interstitial pneumonitis or fibrosis, or both, are also common manifestations. Fever is rarely prominent.

The severity of these chronic pulmonary reactions and the degree of their resolution appear to be related to the duration of therapy after the first clinical signs appear. Pulmonary function may be permanently impaired even after cessation of nitrofurantoin therapy. This risk is greater when pulmonary reactions are not recognized early.

Dermatologic reactions: Maculopapular, erythematous, or eczematous eruption, pruritus, urticaria, and angioedema.

Other hypersensitivity reactions: Anaphylaxis, asthmatic attack in patients with history of asthma, cholestatic jaundice, hepatitis, including chronic active hepatitis, drug fever, and arthralgia.

Hematologic reactions: Hemolytic anemia, granulocytopenia, leukcpenia, eosinophilia, and megaloblastic anemia. Return of the blood picture to normal has followed cessation of therapy.

Neurological reactions: Peripheral neuropathy, headache, dizziness, nystagmus, and drowsiness

Miscellaneous reactions: Transient alopecia. As with other antimicrobial agents, superinfections by resistant organisms may occur. With Macrodantin, however, these are limited to the gentourinary tract because suppression of normal bacterial flora elsewhere in the body does not occur.

### Eaton Laboratories Inc.

A subsidiary of MortonNorwich Products, Inc., Manatí, Puerto Rico 00701

Indiaes medical inquiries to: Norwich-Eaton Pharmaceuticals, Medical Department, Norwich, New York 13815

## CLINICAL BIOSTATISTICS:

## here's why you'll benefit from this book

- authoritative articles from <u>Clinical Pharmacology and</u> Therapeutics
- clear and easy-to-read explanations of essential statistical concepts
- provocative insights into the common sense and science behind statistical data

### CLINICAL BIOSTATISTICS

This unique book critically examines the entire field of clinical biostatistics. It presents a series of original articles that first appeared over a five year period in *Clinical Pharmacology and Therapeutics*. Widespread reader acclaim and the timeliness of the subject prompted publication of the essays into convenient book form.

The essays are logically arranged into 29 chapters and organized into five major sections, each preceded by brief commentary written especially for the book. You'll find informative discussions on the diverse statistical techniques used in medical practice and research; research and design problems; presentation of data; and methods of data analysis. Dr. Feinstein has reorganized his original articles to provide you with a completely current guide to the biostatistics used in both clinical and investigative situations. He also offers valuable insights into topics either totally neglected or inadequately covered in conventional texts. Throughout, discussions are written in lively prose style, which makes the subject both interesting to read and easy-to-understand. Why not benefit from Dr. Feinstein's expert guidance firsthand-order your copy of CLINICAL BIOSTATISTICS today!

By Alvan R. Feinstein, M.D., 1977, 468 pages plus FM I-XIV, 6-7/8" x 10", 10 illustrations. Price, \$21.50

### **ORDER BY PHONE!**

Call toll free (800) 325-4177 ext. 10. In Missouri call collect—(314) 872-8370 ext. 10 during normal business hours.

A80794
Price effective in U.S.A. only.

MOSBY TIMES MIRROR

THE C V MOSBY COMPANY

11830 WESTLINE INDUSTRIAL DRIVE
ST LOUIS MISSOURI 63141

## American Journal of Obstetrics and Gynecology

volume 138 number 4

Остовек 15, 1980

## **CLINICAL OPINION**

This section reports opinion on the handling of clinical situations, i.e., the clinical diagnosis and management of certain disease entities. Papers should range from eight to twenty typed pages, including illustrations, tables, and figures which clarify the author's management. References are limited to sixteen citations. Mail to Frederick P. Zuspan, M.D., Editor.

## What can be done to prevent congenital toxoplasmosis?

CHRISTOPER B. WILSON, M.D.\*
JACK S. REMINGTON, M.D.
Stanford, California

There is a great deal of confusion within the medical and lay communities regarding *Toxoplasma* infection in the pregnant woman. Many physicians are not aware of the significance of this infection in pregnant women or of measures that may decrease the likelihood of the birth of an infant with congenital toxoplasmosis. Data regarding the morbidity, incidence, cost, and measures for the prevention of congenital toxoplasmosis are discussed. I.A.M. J. OBSTET. GYNECOL. 138:357, 1980.)

It is an established fact that primary infection with *Toxoplasma* acquired during pregnancy can result in congenital infection in the offspring or in spontaneous abortion.<sup>1, 2</sup> It is *not* an established fact that latent

From the Department of Medicine, Division of Infectious Diseases, Stanford University School of Medicine, and the Division of Allergy, Immunology, and Infectious Diseases, Palo Alto Medical Research Foundation.

Supported by Grant A104717 from the National Institutes of Health.

Presented in part at the Sixth European Congress of Perinatal Medicine, Vienna, Austria, August 29-September 1, 1978. chronic) infection with *Toxoplasma* during pregnancy can result in congenital infection in the offspring.<sup>2-4</sup> Thus we will limit our discussion to the population we consider pertinent in regard to the prevention of con-

Reprint requests: Jack S. Remington, M.D., Palo Alto Medical Research Foundation, 860 Bryant Street, Palo Alto, California 94301

\*Recipient of Postdoctoral Fellowship Award A105632 from the National Institutes of Health and recipient of the Edith Milo Fellowship. Present address: Department of Pediatrics, University of Washington School of Medicine and the Children's Orthopedic Hospital and Medical Center, Seattle, Washington.

**Table I.** Complications developing in 13 children with congenital toxoplasmosis who had no stigmata of congenital toxoplasmosis at birth\*

Complication	No. of affected children
Unilateral macular chorioretinitis with	3†
unilateral blindness (visually handi- capped)	,
Chorioretinitis (unilateral or bilateral) without substantial visual impairment	8
Severe retardation requiring state- supported care	1
Moderate mental retardation	1
Sensorineural hearing loss (not functionally significant)	3‡
None	. 2
Total No. of children with one or more sequelae	11 (85%)

<sup>\*</sup>Ages at time of last follow-up = 3.5 to 11.2 years.

genital toxoplasmosis, that is, pregnant women who acquire the primary infection during gestation.

### Morbidity

Congenital toxoplasmosis causes significant morbidity in the children it affects. At least 8% of newborn infants with congenital toxoplasmosis are severely damaged due to involvement of the central nervous system and eyes.5 The remainder are either asymptomatic or have only mild abnormalities in the first year of life. One would assume that only a relatively small fraction of this latter group represents a significant problem. This is not the case. Data indicate that a substantial proportion of the asymptomatic infants subsequently will develop serious untoward sequelae of the congenital infection. 4-5 We and our colleagues from the University of Alabama have performed follow-up studies of children with congenital toxoplasmosis from throughout the United States. 5a To date, 13 children who had no signs of congenital toxoplasmosis as neonates have been carefully followed prospectively (Table I). Of these 13 children, 85% have developed untoward sequelae; in three cases, these sequelae have already resulted in functional impairment. Three of the children who developed chorioretinitis have had recurrent episodes of active chorioretinitis. Also, each of the six children who had intelligence testing performed more than once had a drop in I.Q. between the initial and the subsequent tests. It is likely that even further deterioration of the clinical status of these 13 children will occur with subsequent follow-up evaluation. Many of these children received specific treatment during the first year of life. Since treatment may have had a beneficial effect, these data may underestimate the true incidence of serious sequelae that occur in the majority of infants with congenital toxoplasmosis—those who go unrecognized and therefore untreated. Because of the small numbers of children studied, these data can only be considered as estimates of the outcome in such children; however, it appears that toxoplasmosis is a serious problem not only in the infant who has clinically apparent damage at the time of birth but also in the infant whose infection is subclinical during the newborn period whether or not treatment was given.

We could find only two groups who concluded that "congenital toxoplasmosis rarely causes serious damage to the child."<sup>3–6</sup> The lack of detailed intellectual, <sup>3–6</sup> ophthalmologic, <sup>6</sup> and neurologic <sup>6</sup> testing, the brief duration of follow-up, and the difficulties associated with interpretation of their serologic data may account for their differing conclusions. In fact, two thirds of the children from one of these studies have now developed chorioretinitis. <sup>7</sup>

### Incidence

The calculated seroconversion rate among women of childbearing age in the United States is approximately 0.8% per year (range 0.25% to 1.2% in six cities). One would anticipate from this figure that of every 1,000 pregnant women in the United States, six will acquire primary infection with Toxoplasma during a 9-month gestation. Approximately 45% of women who acquire the primary infection during pregnancy and who are not treated will give birth to congenitally infected infants.5 Thus the expected incidence of congenital toxoplasmosis is 2.7 per 1,000 live births. In the two prospective studies performed in the United States from which one can obtain accurate and carefully qualified data,8-9 the observed incidence of congenital toxoplasmosis was 1.1 per 1,000 live births. Because of methodologic limitations, the incidence figures may be falsely low in both studies. Nevertheless, we shall use this lower figure for purposes of our discussion.

## Cost

Of all children born with congenital toxoplasmosis, approximately 8% are severely affected,<sup>5</sup> and the remainder with mild disease or subclinical infection at birth are at risk for late sequelae. We have used the data from the children we have studied<sup>5a</sup> to estimate the frequency of sequelae in children born with subclinical infection (Table I).

The cost estimates for special care of children with congenital toxoplasmosis, presented in Table II. are based on figures provided in a 1975 cost-benefit analysis done for congenital rubella in the United States<sup>10</sup>

<sup>†</sup>Includes one severely retarded child.

<sup>‡</sup>All three have chorioretinitis as well.

Table II. Lifetime cost for special services for 3,300 children with congenital toxoplasmosis born in the United States each year

Service required	% Utilization*	Cost of service†	Average cost .per child‡	Total cost§
Aid to totally disabled	2.4	$44.875/yr \times 44 yr = 214.500$	\$5,148	\$16,988,400
Special schooling for visually handicapped	14.2	$\$7.500/\text{yr} \times 10 \text{ yr} = \$75,000$	\$10,650	\$35,145,000
Special schooling for moderately retarded	.7.1	$3,500/\text{yr} \times 15 \text{ yr} = 52,500$	\$3,728	\$12,302,400
Institutional or state-supported foster care for severely retarded	15.1	$$7,800/\text{yr} \times 40 \text{ yr} = $312,000$	\$47,112	\$155,469,600
Yearly ophthalmologic follow-up care	78.0	\$39/yr $\times$ 20 yr = \$780 Total	\$608 \$67,246	\$2,006,400 \$221,911,800

<sup>\*</sup>Based on institutional or foster care for approximately 8% of ch.ldren with severe disease at birth (Desmonts and Couvreurs), and outcome of remaining 92% based on follow-up data in Table I. The one unilaterally blind child in Table I who was severely retarded is only included as a child requiring institutional or state-supported foster care. The other two children with unilateral blindness are considered moderately visually handicapped.

and on current costs for services in California after discounting these costs by the difference in the appropriate segment of the consumer price index between 1975 and 1978.\* Direct costs for increased acute care hospitalizations, minor learning disabilities, and behavior disorders were not considered, nor was the indirect cost of decreased lifetime earnings included. Inclusion of costs for these items would have substantially increased the total estimated costs.

The average cost per individual with congenital toxoplasmosis is \$67,246 per lifetime. Of the 3.3 million live births per year in the United States, approximately 3,300 will be infants congenitally infected with *Toxoplasma gondii*. The total cost of caring for these congenitally infected children born each year is \$221.9 million. In a careful analysis published by Frenkel<sup>11</sup> in 1973, the cost for the care of children born with congenital toxoplasmosis was estimated to be lower than our figure; however, at that time health care was less expensive and data regarding the outcome of children born with subclinical infection were not available.

\*Costs for strabismus surgery and eye care were derived by discounting current costs in California (Stanford University Hospital and Palo Alto Medical Clinic) by 16.5% (difference in consumer price index for physicians' fees between October, 1975, and October, 1978; Bureau of Labor Statistics, United States Department of Labor). Disability costs were obtained from the California Departments of Health and Employment Development (August, 1978) and discounted by 22.1% (difference in total consumer price index, October, 1975, and October, 1978; Bureau of Labor Statistics, United States Department of Labor). It must be realized that our estimate is a minimum one, as almost all the children we have used in deriving this figure have not been followed into adulthood and thus may be subject to further clinical deterioration, particularly of visual function.

**Table III.** Methods for the prevention of congenital toxoplasmosis

Prevention of infection in the pregnant woman

Hygienic measures:

Cook meat to ≥66° C, smoke it, or cure it in brine:

Avoid touching mucous membranes of the mouth and eye while handling raw meat.

Wash hands thoroughly after handling raw meat.

Wash kitchen surfaces that come into contact with raw meat. Wash fruits and vegetables before consumption.

Prevent access of flies, cockroaches, etc. to fruits and vegetables.

Avoid contact with or wear gloves when handling materials that are potentially contaminated with cat feces, e.g., cat litter boxes, or when gardening.

Disinfect cat litter box for 5 minutes with nearly boiling water.

Prevention of infection in the fetus

Identification of women at risk by serologic testing.

Treatment during pregnancy—results in  $\simeq 50\%$  reduction in infected infants.

Therapeutic abortion—prevents birth of infected infant only in cases of women who acquired infection in first or second trimester (<50% of cases).

### Prevention

We consider that the aforementioned data on morbidity, incidence, and cost of congenital toxoplasmosis warrant a major attempt to define and initiate means whereby congenital toxoplasmosis can be prevented. Several methods for the prevention of congenital toxoplasmosis have been proposed. Attention to the specific hygienic measures outlined in Table III is the only method available for the *primary* prevention of congenital toxoplasmosis, 11 and it is the responsibility of all physicians caring for pregnant women and women attempting to conceive (women at risk) to in-

<sup>†</sup>All costs are either those quoted by Schoenbaum et al. 10 or current figures from the San Francisco area of California as adjusted downward on the basis of changes in the consumer price index (see text).

<sup>‡</sup>Average lifetime cost per child born with congenital toxop asmosis.

<sup>\$</sup>Lifetime cost for all children born each year with congenital toxoplasmosis.

<sup>||</sup>One third of moderately retarded children have been considered unable to work.10

form them appropriately. The impact of these measures on the incidence of acquired toxoplasmosis in a given population has not yet been defined and will depend on the epidemiology of the infection in that locale. Nevertheless, a substantial effort to educate women at risk and the physicians who care for them is clearly an important aspect of any program for prevention and should be undertaken.

In 1957, Thalhammer<sup>12</sup> suggested that infection of the fetus might be prevented by treatment during gestation of those women who acquire their primary infection with Toxoplasma during pregnancy. This secondary approach to prevention has already been implemented in a number of areas of Europe. The impetus for this is the outcome of two studies that were performed independently by Kräubig<sup>1</sup> in Germany and by Desmonts and Couvreur<sup>2</sup> in France. In the study in Germany, in which Thalhammer's protocol was followed, women who acquired toxoplasmosis during pregnancy were treated with pyrimethamine and sulfonamide after 14 weeks' gestation. Kräubig interpreted his results as showing that treatment reduced the incidence of congenital toxoplasmosis by 70%. The results of initial years of the study in France have been published.2-4 The most recent data in this study, which Desmonts and Couvreur<sup>5</sup> have presented and which one of us (J. S. R.) has recently reviewed independently, reveal that treatment with spiramycin during pregnancy reduced the incidence of congenital toxoplasmosis by 50%. As pointed out by Desmonts and Couvreur, their studies were not strictly controlled. Despite this, the data now accumulated by these investigators overwhelmingly support their contention that treatment during pregnancy significantly reduces the incidence of congenital toxoplasmosis, and such treatment is now being practiced in many countries. (Pyrimethamine and sulfonamides are available in the United States. Spiramycin, a less toxic agent, has not been approved for use in this country.) Although the epidemiology of this infection may differ between France and the United States, we are not aware of any differences in the nature of the infectious process among pregnant women in different geographic areas. Therefore we consider that the data from Paris reflect what can be expected to occur as a result of similar treatment in other locales. It should be emphasized that this treatment is administered to a pregnant woman with a recently acquired (acute) infection in the hope that such treatment will prevent spread of infection to the fetus. The rationale for such treatment is based on the observation that there is a significant lag period between onset of maternal infection and infection of the fetus. The results do not allow for a clear estimate of the effect of treatment

during gestation on the fetus who is already infected when treatment is begun.

Therapeutic abortion may be considered in women who are known to have acquired acute infection during gestation or in whom the likelihood of their having acquired acute infection during gestation is very high. Since abortions are performed as late as 22 to 24 weeks' gestation in the United States, one has time to obtain an initial serologic specimen early in gestation and a follow-up specimen later in gestation in order to define the women at risk of transmitting Toxoplasma to their offspring. However, since only approximately 22% of women who acquire primary Toxoplasma infection during the first 22 to 24 weeks' gestation transmit the infection to their offspring,2 4.5 pregnancies must be terminated to prevent the birth of one infected infant. Even if all women acquiring Toxoplasma during the first two trimesters were to elect abortion, less than one half of all cases of congenital toxoplasmosis would be prevented since more than 50% of infected offspring result from maternal infection acquired in the last trimester. For this reason, treatment of mothers during pregnancy would be a necessary part of any program for secondary prevention, and the efficacy of such treatment should be further evaluated in a controlled manner in this country. Until such data are available, the decision whether to treat with antimicrobial agents or to perform an abortion on a woman suspected of acquiring Toxoplasma infection during pregnancy should ultimately be made by the patient in conjunction with her physician after careful consideration of the potential results of both modalities of intervention.

## Screening

Since approximately 93% of women infected during pregnancy have no clinical illness and since there are no pathognomonic clinical signs of the infection in the adult, diagnosis in the pregnant woman must be made by serologic methods. This makes prospective testing necessary. Despite the variety of serologic tests that are now available and purported to be useful in the early diagnosis of the acute acquired infection, the Sabin-Feldman dye test is the single most reliable test and is, at present, the standard by which all other tests should be evaluated. The conventional indirect fluorescent antibody (IFA) method is more readily available to the practitioner and provides reliable results when carefully performed. However, the use of the IFA test in screening programs is complicated by the fact that many laboratories employ this test without careful standardization of their methods and reagents, and some laboratories use commercially available kits which are unreliable.13 Other diagnostic tests, including the hemagglutination

test, are not reliable in the situation of the pregnant woman. Recently, Desmonts' group and ours, with a modified direct agglutination method which is extremely simple and inexpensive to perform, have obtained highly reproducible and accurate results comparable to those found with the dye test. 13a The IgM fluorescent antibody (IgM-IFA) test provides additional information since it is the most sensitive and accurate test for diagnosing acute infection with T. gondii. 136 This test must be carefully standardized and read only by trained personnel. For information and discussion of the interpretation of serologic test results, the reader is referred to Remington and Desmonts.4

The cost effectiveness of screening women during pregnancy depends on the cost of tests and how frequently they are employed, as compared to the cost to society of caring for the diseased children that would be born in the absence of screening. The approximate cost is \$15 for the Sabin-Feldman dye test or IFA test and \$25 for the IgM-IFA test. If a screening program were to be adopted in the United States, one similar to that outlined by Desmonts and Couvreur<sup>2</sup> in 1974 should be considered. This would include the performance of a serologic test equal in sensitivity, specificity, and reproducibility to the Sabin-Feldman dye test (for example, the IFA test) in all pregnant women as early as possible but at least by 10 to 12 weeks' gestation. (Ideally, testing of all women just prior to pregnancy would identify those at risk.4) Those women who are seronegative initially (approximately 70% in the United States) would then be tested again at 20 to 22 weeks in order to detect those who acquired acute infection during gestation. This would allow sufficient time for a decision on possible therapeutic abortion or for treatment to be started. A third test would be performed near or at term to detect all women who acquire primary infection during pregnancy so that they and their offspring can be identified and appropriately managed.4 A woman whose serum is positive on initial testing would have the IgM-IFA test (or comparable test for IgM antibodies, for example, ELISA) performed on the same serum to detect recent infection.4 If the IgM-IFA test is positive or clinical signs suggestive of acute toxoplasmosis are present, a follow-up IFA test (or comparable test) would be performed to attempt to demonstrate a significant rise in titer. In patients with a positive IFA test of any titer and a negative IgM-IFA test in the first trimester and no clinical signs of acute toxoplasmosis, no further testing would be performed since in the United States the probability of these women being acutely infected is low (probably less than 0.2%). Follow-up testing in such patients and more frequent testing of initially seronegative patients might be cost effective if accurate serologic methods, such as the modified Fulton agglutination test, can be made available at a lower cost.

The current cost for this proposed screening program would be \$43.50 for each pregnancy in which the entire screening program is completed. So that a direct comparison to the 1975 special care cost estimates stated previously can be made, we have discounted screening costs by 29.6% (difference in consumer price index for medical care between October, 1975, and October, 1978; Bureau of Labor Statistics, United States Department of Labor). Such costs then amount to \$110.7 million per year if one assumes 3.3 million live births per year. (This figure can be reduced significantly—see discussion of relative cost effectiveness.) If one assumes that 50% of cases of congenital toxoplasmosis can be prevented,5 a screening program such as the one proposed would be anticipated to save society one half of the \$221.9 million required to care for the children who are born each year with congenital Toxoplasma infection in the United States.

### Relative cost effectiveness

Wide-scale screening is being performed in the United States for many diseases that appear to affect the fetus and newborn infant less commonly than does congenital toxoplasmosis. One such disease is congenital rubella. The cost to society for the care of a child born with congenital rubella has been estimated to be approximately \$25,000 per case. 10 The reason that this figure for congenital rubella is low relative to that for congenital toxoplasmosis is due to the use of a 6% yearly discount rate by Schoenbaum and colleagues 10 to compensate for the nearly 20-year lag time between immunization of infant girls and the subsequent prevention of congenital rubella in their offspring. Rubella occurs in 7 to 8-year epidemic cycles, and since approximately 20,000 cases of congenital rubella occurred during the last epidemic cycle, which peaked in 1964, a similar number of cases had been expected to occur in the time period from 1969 to 1976.14 The fact that an epidemic did not occur has been attributed to the use of vaccine and to the serologic screening program which was performed in pregnant women. At an approximate cost of \$3 per vaccine dose,10 \$225 million were expended for vaccination during that 7-year period; approximately \$210 million were spent additionally on serologic screening in pregnant women during the same period. Therefore, \$435 million were spent to prevent a maximum of 20,000 cases of congenital rubella, which is a cost of \$21,750 per case prevented. It is likely that this figure is an underestimate of the true cost per case prevented since epidemiologic data

'suggest that far less than 20,000 cases were prevented by screening and vaccination. 10, 15

The costs of the rubella screening program and our proposed Toxoplasma screening program seem marginal relative to benefits accrued. Actually, since these figures are based on local laboratory costs for serodiagnosis, they would be considerably less if all tests were performed in a centralized, regional laboratory. If screening for infection with Toxoplasma, rubella virus, and syphilis (another preventable congenital infection) in all pregnant women were organized in a regional fashion, it is likely that all these infections could be diagnosed at a fraction of the present cost. Similar regionalized screening programs to detect inborn errors of metabolism have reduced the cost for the diagnosis of these disorders by 90% or more and in addition have provided a panel of consultants to assist physicians regarding interpretation of test results and management of patients.16 The reliability of the screening tests for these infections and of their interpretation could be more carefully controlled in such a setting. For these reasons, if screening for toxoplasmosis in the United States is to be contemplated, the establishment of such centralized diagnostic and consultative services would be desirable.

At present in the United States, *Toxoplasma* serology is performed haphazardly by laboratories of varying quality for physicians who may understand little of the disease or the tests, and unfortunately, in many cases inappropriate decisions are made on the basis of unreliable information. For these reasons, our present lack of systematic screening, in a setting of sporadic screening which is inadequately supervised, may result in more harm than good.

## Conclusion

Carefully planned, regionalized programs for detecting and treating women who acquire Toxoplasma infec-

tion during pregnancy may prove cost effective and reduce the suffering that now occurs in relation to congenital toxoplasmosis. However, before such programs can be recommended on a national scale, regional screening programs should be instituted on a controlled study basis to provide additional data regarding maternal and congenital Toxoplasma infection in the United States and regarding the benefits and cost effectiveness of such programs. These studies should provide answers to important questions such as: When antimicrobial therapy is administered during gestation to pregnant women who are detected by a screening program such as previously described (in which women are screened less frequently than those in the studies from Paris<sup>5</sup>), how frequently is it effective in preventing transmission of Toxoplasma to the fetus? Which sequelae of the congenital infection can be prevented by postnatal treatment of infected infants? Will the benefits of programs for screening and treatment significantly outweigh the costs? Will the costs of such programs be reduced and their effectiveness enhanced if the programs are performed in conjunction with screening for other preventable infections?

Because congenital *Toxoplasma* infection is a significant public health problem, we urge that such studies be implemented as soon as possible. In the interim, we recognize that many physicians are screening for *Toxoplasma* infection in pregnant women and in women attempting to conceive. We recommend that any serologic test results which suggest that infection was acquired during pregnancy be confirmed and interpreted by a reference laboratory before decisions regarding treatment or therapeutic abortion are made.

We gratefully acknowledge the assistance of Mrs. Anne Scitovsky.

## REFERENCES

- 1. Kräubig, H.: Präventive Behandlung der konnatalen Toxoplasmose, in Kirchoff, H., and Kräubig, H., editors: Toxoplasmose: Praktische Fragen and Ergebnisse, Stuttgart, 1966, Georg Thieme Verlag, pp. 104-122.
- Desmonts, G., and Couvreur, J.: Congenital toxoplasmosis: A prospective study of 378 pregnancies, N. Engl. J. Med. 290:1110, 1974.
- 3. Koppe, J. G., Kloosterman, G. J., de Roever-Bonnet, H., Eckert-Stroink, J. A., Loewer-Sieger, D. H., and de Bruijne, J. I.: Toxoplasmosis and pregnancy, with a long-term follow-up of the children, Europ. J. Obstet. Gynecol. Reprod. Biol. 4:101, 1974.
- 4. Rémington, J. S., and Desmonts, G.: Toxoplasmosis, in Remington, J. S., and Klein, J. O., editors: Infectious Dis-

- eases of the Fetus and Newborn Infant, Philadelphia, 1976, W. B. Saunders Co., pp. 191-332.
- Desmonts, G., and Couvreur, J.: Congenital toxoplasmosis: A prospective study of the offspring of 542 women who acquired toxoplasmosis during pregnancy—pathophysiology of congenital disease, in Thalhammer, O., Baumgarten, K., and Pollak, A., editors: Perinatal Medicine, Sixth European Congress, Stuttgart, 1979, Georg Thieme Publishers, pp. 51-60.
- 5a. Wilson, C. B., Remington, J. S., Stagno, S., and Reynolds, D. W.: Development of adverse sequelae in children born with subclinical congenital Toxoplasma infection, Pediatrics. In press.
- 6. Mau, G., Berger, J., and Piekarski, G.: Toxoplasmose in

- der Schwangerschaft und Kindesentwicklung bis zum 3, Lebensjahr. Mschr. Kinderheilk. 125:433, 1977.
- de Roever-Bonnet, H., Koppe, J. C., and Loewer-Sieger, D. H.: Follow-up of children with congenital Toxoplasma infections and children who became serologically negative after one year of age, all born in 1964-1965, in Thalhammer, O., Baumgarten, K., and Pollak, A., editors: Perinatal Medicine, Sixth European Congress, Stuttgart, 1979, Georg Thieme Publishers, pp. 61-75.
- Alford, C. A., Jr., Stagno, S., and Reynolds, D. W.: Congenital toxoplasmosis: Clinical, laboratory, and therapeutic considerations, with special reference to subclinical disease, Bull. N.Y. Acad. Med. 50:160, 1974.
- Kimball, A. C., Kean, B. H., and Fuchs, F.: Congenital toxoplasmosis: A prospective study of 4,048 obstetric patients, Am. J. Obstet. Gynecol. 111:211, 1971.
- Schoenbaum, S. C., Hyde, J. N., Jr., Bartoshesky, L., and Crampton, K.: Benefit-cost analysis of rubella vaccination policy. N. Engl. J. Med. 294:306, 1976.
- policy, N. Engl. J. Med. **294**:306, 1976. 11. Frenkel, J. K.: *Toxoplasma* in and around us, Bioscience **23**:343, 1973.
- 12. Thalhammer, O.: Die Toxoplasmose bei Mensch und

- Tier, Wien, 1957, Verlag für Medizinische Wissenschaften Wilhelm Maudrich, pp. 1-307.
- Durham, T. M., and Colvin, H. M.: Premarket evaluation of commercial toxoplasmosis indirect fluorescent-antibody reagents, J. Clin. Microbiol. 7:255, 1978.
- 13a Desmonts, G., and Remington, J. S.: Direct agglutination test for diagnosis of Toxoplasma infection: Method for increasing sensitivity and specificity, J. Clin. Microbiol. 11:562, 1980.
- 13b.Welch, P. C., Masur, H., Jones, T. C., and Remington, J. S.: The serologic diagnosis of acute lymphadenopathic toxoplasmosis, J. Infect. Dis. In press.
- Krugman, S., and Katz, S. L.: Rubella immunization: A five-year progress report, N. Engl. J. Med. 290:1375, 1974
- 15. Modlin, J. F., Brandling-Bennett, A. D., Witte, J. J., Campbell, C. C., and Meyers, J. D.: A review of five years' experience with rubella vaccine in the United States, Pediatrics 55:20, 1975.
- Bennett, A. J. E.: New England Regional Newborn Screening Program, N. Engl. J. Med. 297:1178, 1977.

## Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following written statement, signed by one author: "The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C. V. Mosby Company in the event the work is published. The undersigned author warrants that the article is original, is not under consideration by another journal, and has not been previously published. I sign for and accept responsibility for releasing this material on behalf of any and all co-authors." Authors will be consulted, when possible, regarding republication of their material.

## GYNECOLOGY

## Response to repetitive luteinizing hormone—releasing hormone stimulation in hypothalamic and pituitary disease

ANNE COLSTON WENTZ, M.D. RICHARD N. ANDERSEN, Ph.D.

Memphis, Tennessee

The gonadotropin response to 100  $\mu$ g of luteinizing hormone–releasing hormone (LH-RH) administered three times intravenously at 2-hour intervals was measured to ascertain whether this would distinguish between patients with hypothalamic and those with pituitary disease. Responses in two patients with Kallmann's syndrome were compared to those in patients with other forms of hypothalamic or pituitary disease, including weight-loss amenorrhea, panhypopituitarism, and hyperprolactinemia. The conclusion was that a triple-bolus LH-RH test is not adequate to distinguish patients who are potentially treatable with LH-RH from those in whom no stimulation can be anticipated. (Am. J. Obstet. Gynecol. 138:364, 1980.)

INFUSIONS of luteinizing hormone—releasing hormone (LH-RH) or the administration of it in a pulsatile fashion may initiate or restore pituitary gonadotropin output in virtually all patients with pubertal delay or suprapituitary disease. <sup>1-3</sup> As a therapeutic role for LH-RH is developed, a simple test is needed to identify which patients with hypogonadotropic hypogonadism might be responsive to the administration of LH-RH. Tests which have distinguished between hypothalamic and pituitary disease have required either continuous

From the Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, The University of Tennessee College of Medicine.

This work was supported in part by General Clinical Research Center Grant No. RR 00211.

Received for publication February 8, 1980.

Revised May 9, 1980.

Accepted June 10, 1980.

Reprint requests: Anne Colston Wentz, M.D., Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, Tennessee 37232.

infusion of LH-RH for long periods of time<sup>4</sup> or repetitive injections of LH-RH over several days.<sup>5</sup> The major purpose of this study was to validate a shorter test. We have used a repetitive stimulation test performed in 1 day and have not been able to reliably distinguish between patients with hypothalamic and those with pituitary disease.

## Material and methods

Patients. We studied patients with histories and clinical diagnoses suggestive of hypothalamic or pituitary problems. Five patients with secondary amenorrhea due to anorexia nervosa or simple loss of weight were chosen as examples of presumptive hypothalamic disease; these patients had not responded with ovulation to clomiphene citrate, 100 mg daily for 10 days. For comparison, six patients with pituitary diagnoses were studied, including four with pituitary tumors, one with well-documented Sheehan's syndrome, and a hypopituitary dwarf with hypothyroidism. One prolactin-producing pituitary tumor and two chromophobe adenomas were diagnosed by sellar tomography and

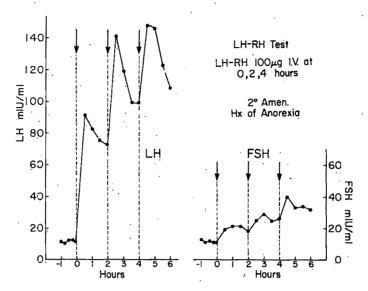


Fig. 1. Case 5. Patient with a history of anorexia nervosa and a 51-pound loss of weight shows increasing LH peaks when tested at 85% ideal body weight.

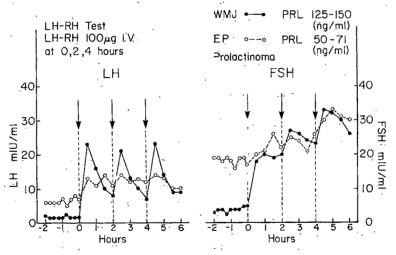


Fig. 2. Patients with pituitary adenomas show a decreasing peak response to repetitive LH-RH stimulation, suggesting an impaired synthesis of gonadotropin.

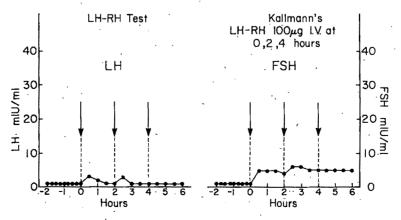


Fig. 3. Case 13. Patient with Kallmann's syndrome showed no evidence of gonadotropin synthesis after three bolus infusion of LH-RH.

Table I. Clinical and diagnostic characteristics of patients with hypothalamic or pituitary disease

	Case No.	Age (yr)	Diagnosis	Duration of amenorrhea (yr)	Maturation index
Hypothalamic	1	24	Hx/anorexia	· 9	0/80/20
dysfunction	2	23	Hx/wt. loss	2	
,	3	27	Wt. loss amenorrhea	3	/0/90/10
	4	26	Wt. loss amenorrhea	3	0/100/0
	5	28	Hx/anorexia	3	82/15/3
Pituitary	6	27	"Prolactinoma"	$BCPs \times 8 yr$	0/75/25
defects	7	54	"Prolactinoma"	Hysterectomy in 1961	30/70/0
	8	63	Chromophobe adenoma	Hysterectomy "years ago"	•
	9	22	Chromophobe adenoma	7	•
	10	69	Sheehan's syndrome	38	
	1 I.	22	Panhypopituitarism	Primary amenorrhea	
Hypothalamic	12	15	Kallmann's syndrome	Primary amenorrhea	
defects	13	17	Kallmann's syndrome	Primary amenorrhea	
"Unknowns"	14	20		Primary amenorrhea	80/20/0
	15	18	?	Primary amenorrhea	78/22/0
	16	25	?	Primary amenorrhea	0/100/0

Hx = Hypothalamic disease; BCP = .

Table II. Results of LH-RH stimulation

Case No.	LH (mIU/ml)	Peak <sub>1</sub>	$Peak_2 \ (mIU/ml)$	Peak <sub>3</sub>	$\Delta_1^*$ $(m$	$rac{\Delta_2}{IU/ml_j}$	Δ <sub>3</sub> )	FSH (mIU/ml)	Peak <sub>1</sub>	$Peak_2$ (mIU/ml)	$Peak_3$	Δ <sub>1</sub>	$\Delta_2$ m $IU/n$	$\Delta_3$
1	3.8	27	41	50	23.2	26	27	9.1	19	30	39	9.9	15	9
2	1.0	27	39	36	26.0	30	22	5.5	12	19	21	6.5	8	6
3	3.3	15	17	14	11.7	9	5	5.0	10	15	18	5.0	5	5
4	1.5	6	10	17	4.5	8	13	1.9	4	6	8	2.1	2	3
5	11.2	91	141	148	79.8	69	49	11.6	21	29	40	9.4	11	14
6	1.2	23	21	23	21.8	13	16	4.0	20	27	33	16.0	7	10
7	6.4	14	14	14	7.6	3	2	18.2	26	26	33	7.8	4	7
8	22.3	67	52	73	44.7	17	21	38.0	56	65	72	18.0	9	11
9	11.5	74	75	78	62.5	22	18	8.5	16	17	19	7.5	1	4
10	6.3	10	18	20	3.7	9	3	13.1	16	18	18	2.9	3	0
11	1.0	1	1	1	0.0	0	0	<1.0	<1	<1	ĺ	0.0	0	0
12	1.0	1	1	1	0.0	0	0	1.0	2	4	3	1.0	2	0
13	<1.0	3	3	<1	2.0	2	0	< 1.0	5	6	5	4.0	2	0
14	6.0	17	12	12	11.0	0	0	5.3	19	22	19	13.7	3	C
15	1.7	7	4	4	5.3	2	I	<1.0	6	6	7	5.0	0	1
16	1.0	12	14	22	11.0	11	14	3.0	' 9	13	18	6.0	6	6

 $<sup>*\</sup>Delta$  = Change in mIU/ml from nadir to peak.

histologically confirmed. One patient (Case 6) with hyperprolactinemia and bony sellar erosion refused operation. Five patients with primary amenorrhea and hypogonadism were studied, two of whom had Kallmann's syndrome; thyroid-releasing hormone (TRH) and insulin tolerance testing indicated an adequate pituitary response. In the other three patients, hypothalamic hypogonadism could not be distinguished from hypopituitary disease (or isolated gonadotropin deficiency), although all had normal thyroid and growth hormone parameters.

Each patient gave informed written consent to the studies, which were approved by the Patient Participation Committee of the University of Tennessee Center for the Health Sciences. The tests were performed in the Clinical Research Center, usually on an outpatient

basis, although selected patients were admitted for further studies.

**LH-RH testing.** An indwelling butterfly needle was used to permit sampling of blood every 15 minutes for a minimum of 2 hours, at the end of which time an intravenous bolus of  $100~\mu g$  of LH-RH was administered. Repetitive doses of LH-RH were administered at 0, 2, and 4 hours; samples of blood for analysis of hormones were obtained at 30, 60, 90, and 119 minutes after each bolus of LH-RH.

No side effects or untoward effects were experienced by any subject.

**Protein hormone radioimmunoassay.** Circulating plasma follicle-stimulating hormone (FSH) and LH were determined as previously described<sup>6</sup> by a two-stage double antibody radioimmunoassay (RIA) tech-

. T	hyroid	Prolactin, basal	Plasma estradiol	
T <sub>4</sub> (μg %)	TSH (mIU/ml)	(ng/ml)	estraaio (pg/ml)	
7.3	1.9	1.8	22	
7.8	1.2	2.3	•	
6.8	1.5	2.5	26	
7.2	1.3	7.5	21	
6.7	2.2	5.2	25	
7.2	6.9	228.0		
6.6	3.4	71.0		
8.3	3.0	8.7	•	
6.9	4.1	6.8		
1.2	2.4	5.8	•	
1.6	< 2.0	1.2		
11.3	<1.0	<1.0	18	
5.7	1.3	1.3		
6.6	4.0	4.0		
9.1	1.5	5.2		
	2.0	2.6		

nique. The Second International Reference Preparation of Human Urinary Menopausal Gonadotropin (2nd IRP-HMG), furnished by the World Health Organization, and LER-907, the Human Pituitary Gonadotropin Reference Preparation, furnished by the Endocrine Study Section of the National Institutes of Health, were used as standard. The minimum detectable concentration was 2 mIU/ml in the LH assay, and 0.6 mIU/ml in the FSH assay. The interassay coefficient of variation was  $\pm 11\%$  for the LH assay and  $\pm 12\%$  for the FSH assay.

## Results

The clinical and diagnostic characteristics of patients in each group are shown in Table I, and the gonadotropin findings are shown in Table II.

The five patients with presumptive hypothalamic disease who had either a history of anorexia nervosa or loss of weight showed increasing FSH peaks to the three bolus injections; the second LH peak always exceeded the first, but variable responses were observed after the third injection (Table II; Fig. 1). Baseline LH and FSH both increased.

An impaired response was observed in the patient with Sheehan's syndrome (Case 10); no response was observed, as expected, in panhypopituitarism. Two patients with hyperprolactinemia and two with a chromophobe pituitary adenoma had an initial LH and FSH response to LH-RH but no augmentation thereafter (Fig. 2).

The patients with presumptive hypothalamic disease diagnosed as Kallmann's syndrome had no increased output of gonadotropin after the three bolus injections (Fig. 3).

The three patients with primary amenorrhea in whom either hypothalamic or pituitary disease could have been responsible had completely dissimilar responses. One patient (Case 14) had a delayed first LH peak and no increment in the second LH peak, although FSH increased (Fig. 4); another patient (Case 16) showed some stimulation, but the pattern was similar to that seen in anorexia nervosa.

### Comment

In presumptive hypothalamic disease associated with weight loss, a repetitive stimulation with LH-RH induced an incremental release of gonadotropin; the increased second LH peak and the continued rise in FSH suggested (but did not prove) synthesis of gonadotropin. Viewed alone, these results give hope that repetitive stimulation with LH-RH may test both the release and synthetic function at the level of the pituitary gland.

This supposition is supported by examination of the LH and FSH findings in patients with pituitary disease. Of four patients with a pituitary adenoma (two with and two without hyperprolactinemia), none had increased second or third LH peaks after repetitive stimulation with LH-RH, which suggested that either the elevated prolactin levels or some degree of pituitary damage had impaired the ability to synthesize and/or release gonadotropins. The patient with the 38-year history of Sheehan's syndrome showed a similar response. The patient with panhypopituitarism and dwarfism, and impaired growth hormone and thyroid dynamics, showed no response to LH-RH stimulation, which is indicative of a failure of synthetic function at the level of the pituitary.

The other patients showed the fallacy of this approach to demonstration of synthetic function. Two patients with Kallmann's syndrome showed absolutely no evidence of an increasing LH response after repetitive administration of LH-RH. Patients with Kallmann's syndrome have previously been studied by means of several techniques of long-term or chronic administration of LH-RH, with evidence of a synthetic effect on LH and FSH output.1, 7, 8 The variability of response in three "unknown" patients does not permit the differentiation of hypothalamic from pituitary disease, and does not diagnose an isolated pituitary gonadotropin deficiency, or a hypothalamic form of hypogonadism which might be treatable with LH-RH. Therefore, this repetitive stimulation was inadequate to induce synthetic function at the level of the pituitary.

The purpose of this study was to show how a simple 1-day repetitive stimulation test could distinguish potential responders to LH-RH when LH-RH was administered in a pulsatile fashion as therapy for delayed puberty or as an alternative to the use of Pergonal in resistant forms of hypothalamic disease. Razdan and

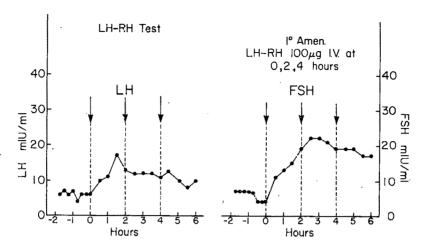


Fig. 4. Case 14. Normal thyroid and adrenal studies, but the delayed LH peak and failure of FSH to continue to rise suggest impaired pituitary synthesis.

co-workers<sup>9</sup> concluded that a 4-hour intravenous infusion of LH-RH seemed to improve differentiation of hypopituitary prepubertal patients from normal children. Snyder and co-workers<sup>5</sup> compared the response to a 250  $\mu$ g bolus LH-RH test before and after daily infusion of 500  $\mu$ g of LH-RH for 7 days to distinguish between hypothalamic and pituitary hypogonadism. This is impractical, but we were unable to demonstrate comparable findings with the use of a shorter 1-day repetitive stimulation. On the other hand, Moltz and co-workers<sup>10</sup> concluded that an increment in the second LH peak after LH-RH stimulation reflected the capacity of the pituitary to synthesize LH, since the first peak represented readily releasable, stored LH. This

may have been true for their patients with polycystic ovarian disease, but our data show that the synthetic capability of the gland cannot be verified by a repetitive stimulation in all cases.

Chronic stimulation with lower doses of LH-RH, ideally administered in pulsatile fashion, may be necessary to induce synthesis. <sup>1-3</sup> We conclude that a repetitive triple-bolus stimulation with LH-RH does not test the synthetic capacity of the pituitary gland in patients who present with hypogonadotropic hypogonadism, and does not select patients for LH-RH therapy.

The Ayerst Company provided the luteinizing hormone-releasing hormone for these tests.

## REFERENCES

- Jacobson, R. I., Seyler, E., Tamborlane, W. V., Gertner, J. M., and Genel, M.: Pulsatile subcutaneous nocturnal administration of GnRH by portable infusion pump in hypogonadotropic hypogonadism: Initiation of gonadotropin responsiveness, J. Clin. Endocrinol. Metab. 49:652, 1979.
- 2. Dickerman, Z., Prager-Lewin, R., and Laron, Z.: The effect of repeated injections of synthetic luteinizing hormone-releasing hormone on the response of plasma luteinizing hormone and follicle-stimulating hormone in young hypogonadotropic-hypogonadal patients, Fertil. Steril. 27:162, 1976.
- Marshall, J. C., and Kelch, R. P.: Low dose pulsatile gonadotropin-releasing hormone in anorexia nervosa: A model of human pubertal development, J. Clin. Endocrinol. Metab. 49:712, 1979.
- Jewelewicz, R., Dyrenfurth, I., Warren, M., Ferin, M., Ans, R., Khalaf, S., and VandeWiele, R.: Effect of single injections and continuous I.V. infusion of synthetic gonadotropin releasing hormone in normal women and patients with primary and secondary amenorrhea, Eur. J. Obstet. Gynaecol. Reprod. Biol., 4/1 suppl: S175, 1974.
- 5. Snyder, P. J., Rudenstein, R. S., Gardner, D. F., and Rothman, J. G.: Repetitive infusion of gonadotropin-

- releasing hormone distinguishes hypothalamic from pituitary hypogonadism, J. Clin. Endocrinol. Metab. 48: 864, 1979.
- Givens, J. R., Andersen, R. N., Wiser, W. L., and Fish, S. A.: Dynamics of suppression and recovery of plasma FSH, LH, androstenedione and testosterone in polycystic ovarian disease using an oral contraceptive, J. Clin. Endocrinol. Metab. 38:727, 1974.
- Antaki, A., Somma, M., Wyman, H., and Van Campenhout, J.: Hypothalamic-pituitary function in the olfactogenital syndrome, J. Clin. Endocrinol. Metab. 38:1083, 1974.
- 8. Oettinger, M., Brunetau, W., Psaroudakis, A., and Greenblatt, R. B.: FSH and LH response to LH-RH in Kallmann's syndrome, Obstet. Gynecol. 47:233, 1976.
- 9. Razdan, A. K., Fang, V. S., Rich, B. H., Britton, H., and Rosenfield, R. L.: Gonadotropin-releasing hormone infusion test in the distinction of hypopituitary patients from normal subjects, Fertil. Steril. 31:507, 1979.
- Moltz, L., Rommler, A., Schwartz, U., Bidlingmaier, F., and Hammerstein, J.: Peripheral steroid-gonadotropin interactions and diagnostic significance of double-stimulating tests with luteinizing hormone-releasing hormone in polycystic ovarian disease, Am. J. Obstet. Gynecol.. 134:813, 1979.

## The standing cystometrogram

STUART A. WEPRIN, M.E. FREDERICK P. ZUSPAN, M.D., F.A.C.O.G. Columbus, Ohio

A major problem in the management of female urinary incontinence is the diagnosis of uninhibited bladder contractions, the recognition of which is important since they are associated with a high failure rate after surgical correction for stress urinary incontinence. Recognition often leads to medical cure and avoids needless surgical procedures, but the diagnosis of uninhibited bladder contractions is often difficult to make without sophisticated prologic instrumentation. This report introduces a simple office test for the diagnosis of uninhibited bladder contractions. With its use, 16% of 91 patients with stress urinary incontinence were found to have uninhibited bladder contractions. (AM. J. OBSTET. GYNECO... 138:369, 1980.)

THE TERM uninhibited neurogenic bladder has been classically used to describe the patient with uninhibited bladder contractions secondary to a neurological defect. However, clinicians have found that many patients with uninhibited bladder contractions do not have demonstrable neurological defects. Hodgkinson and associates¹ popularized this concept by using the term detrusor dyssynergia to describe female patients with uninhibited bladder contractions and no demonstrable neurological defects. Since then the terms bladder hyperreflexia, irritable bladder, and unstable bladder have also been used to describe these patients.

Uninhibited bladder contractions are present in 6% to 66% of urinary incontinent females. 1-4, 6 The importance of making a diagnosis of uninhibited bladder contractions prior to operation is apparent, since they are associated with a poor surgical outcome. 1, 3, 6, 7 Preoperative recognition of uninhibited bladder contractions may lead to medical cure and thus avoid needless surgical procedures. The history and physical examination may suggest a diagnosis of detrusor dyssynergia, but without an objective demonstration of uninhibited bladder contractions the clinician may make an erroneous diagnosis. The use of sophisticated urologic instrumentation is often impractical. This report introduces a simple office test for the diagnosis of uninhibited bladder contractions.

From the Department of Obstetrics and Gynecology, Ohio State University College of Medicine.

Received for publication June 15, 1979.

Revised March 26, 1980.

Accepted June 18, 1980.

Reprint requests: Stuart A. Weprin, M.D., 2200 Medical Building, 2200 Philadelphia Dr., Dayton, Ohio 45406.

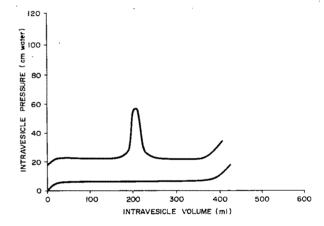


Fig. 1. The top cystometrogram was obtained from an incontinent female patient in the standing position. Notice the uninhibited bladder contraction. The bottom curve is a supine cystometrogram from the same patient. Treatment with anticholinergic medicine resulted in a cure of the incontinence.

## Material and methods

The study population consisted of 91 female patients with symptomatic urinary incontinence, and 11 continent control female patients without urologic symptoms. The patients ranged in age from 22 to 86 years. All patients were evaluated with both standing and supine filling cystometrograms.

The procedure included cystometrography performed with a Foley catheter connected to a plastic polyethylene tube to a carbon dioxide cystometer. Filling rates of the bladder were 120 ml/min. All patients were first tested standing, then supine. Those patients with infected urine were excluded from the study.

Uninhibited bladder contractions of at least 30 mm of mercury in intensity were considered to be clinically significant (Fig. 1). There is no problem in distinguish-

370 Weprin and Zuspan

**Table I.** Findings by standing and supine cystometrography in 91 patients with urinary incontinence

Findings by cystometrography	Type of cystometrography	
	Standing	Supine
Normal	76 (84%)	86 (95%)
Uninhibited bladder contractions	15 (16%)	5 (5%)

**Table II.** Comparison of findings by cystometrography and history of previous repair for incontinence (N = 91)

Findings by cystometrography	Previous repair	No previous repair
Normal	18 (75%)	58 (87%)
Uninhibited bladder contractions	6 (25%)	9 (13%)

ing true bladder activity at 30 mm Hg from increased intra-abdominal pressure secondary to movement of the patient or the Valsalva maneuver. All patients were instructed to inhibit any urge to void, and Valsalva maneuvers were not performed. The tests were complete when the third segment of the cystometrogram was reached or the patients became too uncomfortable. The uncomfortable sensation was experienced most commonly with a volume between 300 and 400 ml.

Urethroscopy, cystoscopy, and urethral pressure profiles were performed when indicated, but only after the cystometric studies were completed.

Statistical analyses were performed in the following manner. A test for differences between correlated proportions was used to determine the superiority of either the standing or supine cystometrogram. All other tests for association were made using chi-square. When statistical assumptions underlying the chi-square test were not fully met, Fischer's exact probability test was used to confirm the chi-square results.

### Results

Of the ninety-one patients studied, 15 had uninhibited bladder contractions. If only supine studies had been performed, two thirds of the patients with uninhibited bladder contractions would have been missed. Sixty-seven percent of those with uninhibited bladder contractions were only detected in the standing position. Standing cystometrography produces findings significantly different from those with supine cystometrography (P < 0.05) and is recommended as the procedure of choice. No patient had normal findings

with the standing test when the supine test gave abnormal findings. All controls had normal cystometrograms in both the standing and supine positions (Table I).

Seventy-four percent of patients studied had not undergone a previous operation for incontinence, and 13% of these had uninhibited bladder contractions. Twenty-six percent of patients studied had had a previous repair, and 25% of these had uninhibited bladder contractions. We found no significant association in terms of the incidence of uninhibited bladder contractions (P > 0.05) between those who did and those who did not have previous surgical repairs (Table II).

Patients with uninhibited bladder contractions ranged in age from 25 to 67 years, and in parity from 0 to 4. All except three had descent of the urethrovesicle angle. It should be noted that in many the descent was not greater than a first-degree cystourethrocele. All 15 patients with uninhibited bladder contractions had normal findings on neurological examination (Table III).

Table IV addresses the question of the value of history in differentiating patients with uninhibited bladder contractions from patients with urinary stress incontinence. Significant differences were found for symptoms of urgency, enuresis, and incontinence, whereas no significant differences were found for frequency, nocturia, and frequent infections of the urinary tract between patients with uninhibited bladder contractions and patients with stress incontinence ( $P \le 0.05$ , Table V). However, for any one patient, this difference had little diagnostic value. Most patients with stress incontinence had at least two or more complaints traditionally associated with uninhibited bladder contractions.

Table VI illustrates our preliminary results in treating the patients with uninhibited bladder contractions. Ten patients were treated without surgical procedures. Four of these 10 experienced marked improvement of their condition, three noted partial improvement, and the condition in three was considered to be unimproved since they did not return for follow-up. Of three patients treated with fascial slings, one had marked improvement, another noticed no change in symptoms, and the third experienced increased incontinence. Her increased symptoms may have been secondary to a reduced capacity of the bladder. One patient's condition improved after a hysterectomy for adenomyosis, the pressure from the enlarged uterus may have caused the bladder irritability. Another patient was asymptomatic after repair of her urethral diverticulum. Her uninhibited bladder activity may have been secondary to the recurrent urethritis associated with the diverticulum.

Posttreatment cystometrography was performed on

Table III. Summary of pertinent clinical findings in 15 patients with uninhibited bladder contractions

Patient	Age (yr)	Vaginal deliveries	Urethrovecical angle	Previous repair	Other
1.	30	3 .	Descent	None	None
2.	50	. 4	Descent	None	None
3.	55	4	Descent	None	Multiple sclerosis
4.	.59	3	Descent	Vaginal Abdominal	Previous repair of lumbar disc
5.	25	4	Normal	None	Previous kidney stone
6.	41	0 .	Norma.	Anterior repair MMK	None ,
8.	40	3	Descen:	None	Seizure disorder
9.	60	. 1	Descent.	Anterior	None
9. 10.	47	2	Descent	MMK Anterior repair	Sciatica on left side
11.	59	0	Normal	None	None '
12.	71	· 3	Descent	Anterior repair	None
13.	37	<b>5</b> · '	Descent	Anterior repair	None
14.	67	2	Descent	None	None
15.	30	5	Normal	None	Urethral diverticulum

MMK: Marshall-Marchetti-Krantz procedure.

Table IV. Comparison of historical findings in patients with uninhibited bladder contractions and in patients with stress incontinence

Patient category	Frequency (%)	Urgency (%)	Nocturia (%)	Enuresis (%)	Two or more infections of Urinary tract (%)	Incontinence characterized by a continuous stream of H <sub>2</sub> O (%)
Uninhibited bladder contractions (N = 15)	. 80	100	80	47	47	27
Stress incontinence $(N = 76)$	69	72	80	16	22	1
,	P > 0.05	P ≤ 0.05	P > 0.05	P ≤ 0.05	$P \ge 0.05$	$P \leq 0.05$

several of the patients, and the findings tended to correlate with the clinical response. Four patients whose condition improved with medical management showed either a reduction in or total absence of uninhibited bladder contractions. One patient who had been successfully treated with a fascial sling had a normal follow-up cystometrogram, and another patient who had been successfully treated with a hysterectomy had a normal follow-up cystometrogram. Finally, the cystometrogram of the patient with a repaired urethral diverticulum showed a marked improvement in the condition of the bladder.

#### Comment

The importance of cystometry in the evaluation of female incontinence is obvious. The primary objective is the identification of the patient with uninhibited bladder contractions, so that surgical procedures can be used to provide maximum benefit. Since we have been unable to identify by history and physical examination those patients who do not need cystometry, we recommend that all patients should undergo this procedure as part of a complete evaluation of urinary incontinence. Turner Warwick<sup>8</sup> was also unable to separate by history those patients with uninhibited bladder contractions from the patients with urinary stress incontinence. Although the histories of some patients will seem to be clear, more commonly, the patients present with a complex of mixed symptoms. This is especially true for those patients who have either more pronounced disease or recurrent disease. This problem exists because the uninhibited bladder will be stimulated to contract by the same Valsalva maneuvers which will produce incontinence in patients with weak sphincters.

Because human beings are erect mammals, they have problems that relate to gravity, and since most patients experience their incontinence in the erect position, it seems logical to test them in that position.

Standard supine cystometry will reveal less than half of the patients with uninhibited bladder contractions.8-10 Provocative measures, including a change

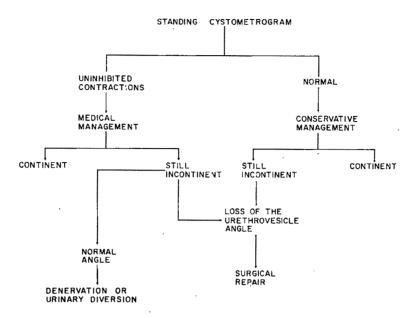


Fig. 2. Management of the female patient with incontinence.

**Table V.** Comparison of historical findings in patients with uninhibited bladder contractions and in patients with stress incontinence

•	Frequency-urgency/ Nocturia-enuresis/ Urinary tract infections/Stream			
Patient category	Fewer than two Complaints (%)	Two or more Complaints (%)		
Uninhibited bladder contractions	0	100		
Stress incontinence	25	75		

from supine to upright position, Valsalva maneuvers, and walking in place, have been used to elicit uninhibited bladder contractions. Such maneuvers require simultaneous measurements of rectal pressure in order to determine true bladder activity. We have found that the erect filling cystometrogram eliminates the need to perform provocative maneuvers and simplifies the study of bladder dynamics.

The etiology of the uninhibited bladder contractions dictates the management of the patient. If the urine is infected, it must be treated prior to repeated cystometrography. The infection is the cause of the uninhibited bladder contractions in some patients, whereas in others it is the result. The uninhibited bladder contractions may also be secondary to neurological disease, common examples of which are lumbar disc herniation, multiple sclerosis, cerebrovascular accident, central arteriosclerosis, and brain tumor. All of these have in common the loss of corticospinal regulation. (The infant bladder is a classic example of this.) A high index

**Table VI.** Results of treatment in 15 patients with uninhibited bladder contractions

Treatment	No.	Results
Medical management	10	7 Improved
_	•	3 No change
Surgical management		Ŭ
Fascial sling	3	1 Improved
G		1 Worse
		1 No Change
Hysterectomy	1	Improved
Repair of urethral	1	Improved
diverticulum	-	- Provide

of suspicion of a neurological lesion is necessary in patients with uninhibited bladder contractions. However, in most patients with uninhibited bladder contractions, a detailed neurological evaluation seldom reveals neurological lesions. Obstruction of outflow is a common cause of bladder instability in men. Recent literature suggests that urethral stenosis may also be a causative factor in women.<sup>14</sup> We routinely perform urethral dilations in patients with uninhibited bladder contractions whose urethra will not admit a No. 16 French catheter. Although unsupported by objective literature, the possibility must also be considered that bladder instability is related to hormonal factors, or perhaps is secondary to atrophic urethritis or a primary bladder effect. This is most commonly seen in the menopausal patient with atrophic vaginal mucosa, thus indicating they may benefit from a trial of estrogens. The dosage should be one that will not produce stimulation of the uterus. A commonly accepted regimen is to use conjugated estrogens on weekdays only.

In those patients who have no demonstrable etiology for the uninhibited bladder contractions, treatment should be directed at controlling incontinence by suppressing bladder activity. Smooth muscle relaxants (flavoxate hydrochloride, dicyclomine hydrochloride) and anticholinergics (propantheline) are often useful in suppressing uninhibited bladder contractions. Oxybutynin chloride both induces smooth muscle relaxation and exerts an anticholinergic effect, and seems to be the most effective drug available, although few controlled studies have been done on it. In those patients with frequent infections of the urinary tract, we have found that the maintenance of sterile urine by continuous administration of antibiotics avoids unnecessary therapeutic delays secondary to infections of the urinary tract. Prolonged distention of the bladder, bladder retaining programs, psychotherapy, biofeedback, and surgical treatment that includes bladder transections and denervation procedures15, 16 have been advocated as possible treatment modalities. Finally, urinary diversion may be considered as a final procedure in some patients. These forms of therapy all seem heroic and underscore the importance of proper diagnosis, follow-up, medical therapy, and the realization of the complicated nature of the problem.

In those patients with both uninhibited bladder contractions and urinary stress incontinence, the former should be treated first. After the cystometrogram demonstrates suppression of uninhibited bladder contractions, a reassessment of the patient's symptomatology is in order. If incontinence is still a problem and an anatomic defect exists, then a surgical repair is indicated. Occasionally, a surgical repair may be attempted in the event of unsuccessful medical management. This should be done only if an anatomic defect exists and the patient is willing to accept a higher failure rate (Fig. 2).

Patients with uninhibited bladder contractions do not always present with urinary incontinence. Their primary symptomatology may be recurrent infections of the urinary tract. Since we have begun testing continent women with urinary symptoms, such as urgency, frequency, and nocturia, we have found that some of these patients have uninhibited bladder contractions. Our findings in these women will be the subject of a later report.

We wish to thank Janice Bloomfield for assisting us in setting up the Urodynamics Laboratory at The Ohio State University Hospital, and Sue Martin for her help in preparing the manuscript.

#### REFERENCES

- Hodgkinson, C. P., Ayers, M. A., and Drukker, B. H.: Dyssynergic detrusor dysfunction in the apparently normal female, Am. J. Obstet. Gynecol. 87:717, 1963.
- Beck, R. P.: Urinary stress incontinence, Ob-Gyn Digest 15:19, 1976.
- Arnold, E. P., Webster, J. R., Loose, H., Brown, A. D. G., Warwick, R. T. T., Whiteside, C. G., and Jequier, A. M.: Urodynamics of female incontinence: Factors influencing the results of surgery, Am. J. Obstet. Gynecol. 117:805, 1973.
- Aldridge, C. W., Beaton, J. H., and Nazig, R. P.: A review of office urethroscopy and cystometry, Am. J. Obstet. Gynecol. 131:432, 1978.
- Rivard, D. J., and Woodruff, M. W.: Modern urodynamic evaluations in the urologist's office, J. Urol. 120:732, 1978.
- Bates, C. P., Loose, H., and Stanton, S. L. R.: The objective study of incontinence after repair operations, Surg. Gynecol. Obstet. 136:17, 1973.
- Beck, R. P., Arnusch, D., and King, C.: Results in treating 210 patients with detrusor overactivity incontinence of urine, Am. J. Obstet. Gynecol. 125:593, 1976.

- 8. Warwick, R. T. T.: Some clinical aspects of detrusor dysfunction, J. Urol. 113:539, 1975.
- 9. Mayo, M. E.: Detrusor hyperreflexia: The effect of posture and pelvic floor activity, J. Urol. 119:635, 1978.
- 10. Arnold, E. P.: Cystometry—Postural effects in incontinent women, Urol. Int. 29:185, 1974.
- 11. Jeffcoate, T. N. A., and Francis, W. J. A.: Urgency incontinence in the female, Am. J. Obstet. Gynecol. 94:604, 1966
- 12. Lapides, J., and Costello, R. T.: Uninhibited neurogenic bladder: A common cause for recurrent urinary infection in normal women, J. Urol. 101:539, 1969.
- 13. Rees, D. L. P., Wickham, J. E. A., and Whitefield, H. N.: Bladder instability in women with recurrent cystitis, Br. J. Urol. 50:524, 1978.
- 14. Van Rooyen, A. J. L., and Liebenberg, H. C.: A clinical approach to urinary incontinence in the female, Obstet. Gynecol. 53:1, 1979.
- Ingelman-Sundberg, A.: Partial denervation of the bladder, Acta Obstet. Gynecol. Scand. 38:487, 1959.
- Diokno, A. C., Vinton, R. K., and McGillicuddy, J.: Treatment of the severe uninhibited neurogenic bladder by selective sacral rhizotomy, J. Urol. 118:299, 1977.

### The effect of radical hysterectomy on bladder physiology

J. PETER FORNEY, M.D.

Dallas, Texas

Voiding dysfunction and vesical sensation and continence problems were serially evaluated by history and CO<sub>2</sub> cystourethroscopy in 22 women who had undergone a radical hysterectomy. In 11 of these women, the cardinal ligaments had been divided completely, and in the other 11, the inferior 1 to 2 cm of these ligaments had been spared. Sat sfactory voiding occurred significantly earlier (20 versus 51 days) in women who had had an incomplete transection. Vesical sensation was diminished in all subjects, but the magnitude of the sensory deficit was no greater in those who had had a complete transection. Stress incontinence occurred more frequently in those who had had a complete transection. Hypertonic cystometric measurements and decreased intraurethral pressure were common postoperative findings, and it is postulated that sýmpathetic denervation is responsible for both of these alterations. (Am. J. Obstet. Gynecol. 138:374, 1980.)

IMPROVEMENTS in operative technique, anesthesia, antimicrobials, and the clinical laboratory, combined with restrictive use of radical hysterectomy to healthier women with clinically localized cervical cancer, have markedly decreased the frequency of operative death, serious infection, and urinary fistulas. However, the frequency of bladder dysfunction after radical hysterectomy has not been similarly reduced and is now recognized as the most common complication of radical hysterectomy. For years, patients have a diminished awareness of vesical distention and may void "by the clock" rather than by urge. Months may pass before patients can initiate and/or successfully complete micturition. Manual suprapubic pressure and vigorous straining are often the ultimate solution to nearly complete evacuation of the bladder, and a small percentage of women must even resort to periodic selfcatheterization. Postoperative urinary stress incontinence seems also to occur in a disproportionately high percentage of patients.

The incidence, severity, and pathogenesis of these alterations in bladder function have been the subject of

From the Cecil H. and Ida Green Center for Reproductive Biology Sciences, and the Department of Obstetrics and Gynecology, The University of Texas Health Science Center at Dallas.

Received for publication February 15, 1980.

Accepted June 11, 1980.

Reprint requests: J. Peter Forney, M.D., Department of Obstetrics and Gynecology, The University of Texas Health Science Center at Dallas, 5323 Harry Hines Blvd., Dallas, Texas 75235.

past reports. 1-10 This article readdresses these issues; however, the method of evaluation, results, and conclusions are, in some respects, unique.

#### Material and method

Between June 1, 1976, and May 30, 1979, I performed radical hysterectomy and pelvic lymphadenectomy on 37 women. Twenty-two underwent preoperative and serial postoperative CO<sub>2</sub> cystourethroscopy with simultaneous evaluation of the urethral and bladder pressure profile (Cu-UBPP). A Robertson 18guage urethroscope and a Browne CO<sub>2</sub> Cystometry Moniter, Model CR-2, were used to inspect the lower urinary tract and record urethral and vesical pressures. A complete urinary history was taken and intravenous pyelography, urine culture, and residual urine measurement were routinely performed preoperatively. Relevant clinical characteristics of the study group are detailed in Table I. Two women had a preoperative history compatible with mild stress urinary incontinence, and one woman related a history of longstanding urinary urgency and frequency. No patient had a positive preoperative urine culture, a residual urine greater than 10 ml, or an abnormal intravenous pyelogram.

A pelvic lymphadenectomy with radical hysterectomy similar to that described by Meigs<sup>11</sup> was performed in 11 of the 22 women studied. In these 11 women, the cardinal ligaments were exposed by dissection of the pararectal and paravesical spaces and were divided to the pelvic diaphragm (Fig. 1). In the other 11 women, the inferior 1 to 2 cm of each cardinal liga-

Table I. Clinical characteristics

Patients	Age (yr)	Parity	Weight (lb)	Diagnosis	History of Incontinence
H. C.	33	2	153	Stage IB (Occ) squamous cell carcinoma of cervix	"Stress"
B. E.	29	2	123	Stage IB (Occ) squamous cell carcinaoma of cervix	None
J. C.	49	0	116	Stage IB (Occ) squamous cell carcinoma of cervix	"Urge"
D. G.	32	5	170	Stage IB squamous cell carcinoma of cervix	None
В. Т.	25	1	118	Stage IIA adenocarcinoma of vagina	None
L. L.	40	5	138	Stage IB adenocarcinoma of cervix	None
P. M.	24	3	181	Stage 1B squamous cell carcinoma of cervix	None
A. D.	37	1	112	Stage IB squamous cell carcinoma of cervix	None
E. R.	32 ·	5	157	Stage IB squamous cell carcinoma of cervix	None
B. P.	31	3	172	Stage IB squamous cell carcinoma of cervix	None
R. N.	34	4	189	Stage IE (Occ) squamous cell carcinoma of cervix	None
M. G.	65	0	114	Stage IB (Occ) squamous cell carcinoma of cervix	None
N. H.	36	2	106	Stage B adenocarcinoma of cervix	None
F. G.	38	3	135	Stage IB adenocarcinoma of cervix	"Stress"
W. C.	37	2	144	Stage IB squamous cell carcinoma of cervix	None
K. M.	36	3	119	Stage 1B squamous cell carcinoma of cervix	None
D. P.	25	0	135	Stage IE squamous cell carcinoma of cervix	None
J. R.	31	2	149	Stage IB squamous cell carcinoma of cervix	None
F. T.	43	4	128	Stage I3 squamous cell carcinoma of cervix	None
M. S.	33	3	104	Stage 🖂 (Ócc) squamous cell carcinoma of cervix	None
L. B.	20	1	205	Stage IB (Occ) squamous cell carcinoma of cervix	None
R. J.	18	1		Stage IB squamous cell carcinoma of cervix	None

Table II. Preoperative Cu-UBBP

Patient	Maximum intraurethral Pressure (cm H₂O)	Volume at first urge (cc of CC <sub>2</sub> )	Volume at painful urge (cc of CO <sub>2</sub> )	Pressure profile
H. C.	90	150	220	No pressure rise
B. E.	135	120	230	No pressure rise
J. C.	100	50	180	No pressure rise Uninhibited contraction at 140 cc of CO <sub>2</sub>
D. G.	100	175	310	No pressure rise
В. Т.	120	100	150	No pressure rise
L. L.	95	180	270	No pressure rise
P. M.	90	150	200	No pressure rise
A. D.	100	110	170	No pressure rise
E. R.	65	110	190	No pressure rise
B. P.	120	120	200	No pressure rise
R. N.	100	125	200	No pressure rise
M. G.	75	150	250	No pressure rise
N. H.	140	180	220	No pressure rise
F. G.	75	120	. 180	No pressure rise
W. C.	90	110	260	No pressure rise
K. M.	110	160	250	No pressure rise
D. P.	120	110	175	No pressure rise
J. R.	120	140	250	No pressure rise
F. T.	115	140	200	No pressure rise
M. S.	90	125	210	No pressure rise
L. B.	125	130	225	No pressure rise
R. J.	130	110	230	No pressure rise

ment was left intact (Fig. 2). In all cases the uterosacral and vesicouterine ligaments were divided lateral to the rectum and bladder as deeply as necessary to equate with the level of transection of the cardinal ligaments. In no case was the superior vesical artery ligated, and in each case the ureter was entirely freed from the cardinal and vesicouterine ligaments. The excised vaginal cuff was approximately 1 cm longer in those patients who had complete transection of the cardinal ligaments. Nonbulky adenocarcinomas confined to the endocervix and Stage IB squamous cell carcinomas of less than 1 cm in maximum diameter were chosen for less radical resection of the cardinal ligaments and vagina.

A No. 16 Foley catheter with a 5 cc balloon was inserted suprapubically in all patients prior to closure of the abdominal wall. There were no serious postopera-

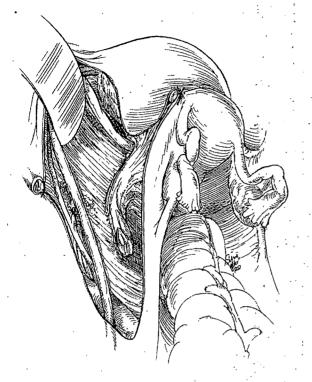


Fig. 1. The cardinal ligament has been divided at the pelvic wall and to the fascia overlying the levator muscle. The paravesical and pararectal spaces are in communication. The ureter has been mobilized from the cardinal ligament and is retracted laterally.

tive infections, or urinary fistulas. One patient, A. D., died 5 months postoperatively, but her death was unrelated to malignancy or the operative procedure. No patient has been lost to follow-up, and all are clinically free of recurrent disease.

Cu-UBPP was performed preoperatively, 10 to 14 days postoperatively, and every 1 to 2 weeks thereafter until the patient was capable of voiding with less than a 50 ml urinary residual. Cu-UBPP was then repeated at 3-month intervals for the first year, and every 6 months thereafter. Follow-up has ranged from 6 to 43 months, with from five to 12 examinations per patient. I performed all examinations and recorded urinary histories at each visit.

The examination routine was as follows: Preoperatively and postoperatively, patients without a catheter were instructed to void; whereupon they were placed in the lithotomy position and the periurethral area was cleansed. After the urethral meatus had been topically anesthetized, the urethroscope, with CO<sub>2</sub> for obturation, was passed through the urethra and into the bladder. The urinary residual was measured and cultured. With the urethroscope held at the vesical neck, the bladder was filled retrogradely with CO<sub>2</sub> at a rate of 120 cc/minute. The volume at first urge and that at



Fig. 2. The inferior segment of the cardinal ligament has been spared and can be seen bridging between the pelvic wall and vagina. The ureter is retracted laterally.

painful urge to urinate were recorded. To check for the normal sphincteric action of the vesical neck and proximal urethra, the endoscope was withdrawn into the upper urethra and the patient was instructed to perform a forceful Valsalva maneuver.

Patients with a suprapubic catheter in situ were examined as outlined above, with the following exceptions: (1) They were not asked to void prior to the examination. (2) If painful urge did not occur before 500 cc of CO2 had been instilled into the bladder, the procedure was terminated for fear of vesical overdistention. (3) After Cu-UBPP, saline solution was placed into the bladder through the suprapubic catheter, and the patient was given the opportunity to urinate. The volume of instilled saline solution varied with individual differences in bladder capacity, but generally ranged from 150 to 250 ml. Five to ten minutes were allowed for voiding and then the residual volume was measured. If the patient was capable of emptying the bladder to all but 50 ml or less of the instilled saline solution, the catheter was clamped and she was allowed to void on her own. Patients were retested within 48 hours to ensure consistently adequate vesical emptying before the catheter was removed. Urobiotics were administered prophylactically for 24 hours after cystourethroscopy, and documented infections were treated for 10 days with appropriate antibiotics.

Table III. Days to spontaneous and satisfactory vesical emptying

Patient	Complete transection of cardinal ligaments	Patient	Incomplete transection of cardinal ligaments
D. G.	32	Н. С.	. 14
B. T.	120	B. E.	28
L. L.	. 84	J. C.	21
A. D.	20	Р. М.	21
E. R.	47	R. N.	16
B. P.	. 80	M. G.	21
W. C.	30	N. H.	14
K. M.	26	F. G.	21
J. R.	63	D. P.	18
Ř. J.	20	M. S.	25
F. T.	35	L.B.	21
	51		20

Mean = p < 0.01.

Table IV. Comparison of preoperative volume at first urge and postoperative volume at first urge on day of catheter removal

Compi	lete transection of cardino	ıl ligaments	Incomp	lete transection of cardin	al ligaments
Patient .	Preop. vol. (cc of CO <sub>2</sub> )	Postop. vol. (cc of CO <sub>2</sub> )	Patient	Preop. vol. (cc of CO <sub>2</sub> )	Postop. vol. (cc of CO <sub>2</sub> )
D. G.	175	250	H. C.	150	220
B. T.	100	>500	B. E.	120	225
L. L.	180	320	J. C.	50	100
A. D.	110	130	P. M.	150	200
E. R.	110	150	R. N.	125	275
B. P.	120	250	M. G.	150	380
W. C.	110	300	N. H.	180	320
K. M.	160	>500	F. G.	120	300
J. R.	140	380	D. P.	110	300
R. J.	110	380	M. S.	125	>500
F. Ť.	140	190	L. B.	130	220

#### Results

Preoperative Cu-UBPP. Table II details the preoperative measurements of maximum intraurethral pressure, volume at first urge, and volume at painful urge for each patient. All volumes were within the range of reported values for normal women.12 Filling pressure was low and did not rise, even at painful urge, in any subject. One patient, J. C., had a history of urinary urgency and frequency and demonstrated an uninhibited detrusor contraction during the early filling phase of the cystometrogram. Her symptoms and the graphic findings suggested that she suffered from the "unstable bladder syndrome."

Time from operation until consistently satisfactory emptying of bladder. The 22 patients were divided into two groups: 11 who had complete transection of the cardinal ligaments, and 11 who had incomplete transection. The mean number of postoperative days before a patient could consistently void with less than a 50 ml urinary residual was fewer, 20 versus 51, in patients who had incomplete transection of the cardinal ligaments (Table III). With the Mann-Whitney test for comparison of nonparametric means, this difference was statistically significant (p < 0.01). Additionally, 7 of 11 women in the group with complete transection of the cardinal ligaments reported, when last examined, that they used accessory somatic muscles to initiate and sustain voiding. This was in contrast to 3 of 11 patients who had the less radical operation.

Bladder sensation. Table IV reflects the magnitude of postoperative vesical sensory change for each pazient. In every instance, there was an increase in the volume required to elicit the urge sensation. The mean increase in CO2 required to elicit the first urge sensation on the day that the catheter was removed was 160 cc among the 11 women who had complete transection cf the cardinal ligaments, as compared to 140 cc in the 11 patients who had incomplete transection. This difference was insignificant.

In addition to a quantitative loss of sensation, there was also a qualitative change. All 22 women reported a postoperative alteration in the perception of vesical dis-

	~								
Table V	Comparison	of pr	eoperative and	mean	nostor	nerstive.	maximiim	intraurethral	pressures
AUDIC V.	COLLIDATION	Or Pr	coperative and	****	POSCO	POLLEGIC	***********	million con con con con	pressures

(	Complete cardinal ligam	ent transection	Incomplete cardinal ligament transection			
Patient	Preoperative (cm H <sub>2</sub> O)	Mean postoperative (cm H₂O)*	Patient	Preoperative (cm H₂O)	Mean postoperative (cm H₂O)†	
D. G.	100	45	Н. С.	150	70	
B. T.	120	60	B. E.	135	115	
L. L.	95	40	J. C.	100	90	
A. D	100	90	P. M.	90 .	80	
E. R.	120	90	R. N.	120	90	
B. P.	120	60	M. G.	120	60	
W. C.	90	60	N. H.	140	120	
K. M.	110	75	F. B.	75	45	
J. R.	. 120	90	D. P.	120	70	
Ř. J.	120	105	M. S.	90	50	
F. T.	115	95	L.B.	125	120	

<sup>\*</sup>Mean decrease = 35.

tention. Typically, bloating and a vague feeling of fullness in the lower abdomen replaced the normal urge to void. Most volunteered that, once they became aware of bladder fullness, severe cramps would shortly follow if they did not soon void. Interestingly, J. C., who had both a history and a cystometrogram compatible with the "unstable bladder syndrome," reported complete resolution of her problem postoperatively. Four women (B. E., B. T., K. M., and M.S.) when last tested were 36, 26, 11, and 5 months removed from the time of their operations and could not appreciate a voiding urge at 500 cc of CO<sub>2</sub>.

Once a patient was capable of emptying the bladder, neither the volume at voiding urge nor the volume at painful urge varied more than 50 cc of CO<sub>2</sub> throughout the period of follow-up, except in two instances. B. E.. at her 18-month examination, and M. G., at her 6-month examination, were found to have lost the voiding urge entirely. Despite the admonition to "void by the clock," these patients had not voided at regular intervals. M. G. regained the voiding urge 20 months postoperatively, but B. E. at her 36 month's visit could not appreciate urinary urgency at 500 cc of CO<sub>2</sub>.

Residual urine. Except in two patients, the values of residual urine decreased progressively in the postoperative period. B. E. and M. G., mentioned previously, demonstrated an increase in residual urine coincident with the discovery of a high-capacity, sensationless bladder.

Stress incontinence and urethral pressure changes. Five women with a negative preoperative history developed urinary stress incontinence postoperatively. Four of the five had undergone the more radical operation. One of two patients with preexisting stress incontinence became considerably more symptomatic, and the other was symptomatically unchanged. Postop-

erative urethroscopy demonstrated a proximal urethral opening with the Valsalva maneuver in each symptomatic patient and in two other patients without a history of incontinence. In all 22 patients, intraurethral pressure maxima were consistently lower postoperatively and did not vary more than 15 cm of H<sub>2</sub>O from one postoperative examination to another. Table V depicts preoperative and mean postoperative maximum intraurethral pressure measurements on each patient. The mean pressure decreases among the two operative groups were similar.

Postoperative bladder pressure profiles (Table VI). In the immediate postoperative weeks, all patients who underwent complete transection of the cardinal ligaments, and 4 of 11 who had incomplete transection, demonstrated a progressive rise in vesical pressure upon filling. Fig. 3 displays preoperative and serial postoperative bladder pressure profiles on a single patient, E. R. All 15 women who developed this unique cystometric pattern had strikingly similar records. Despite the progressive rise in bladder pressure, no patient who had this pattern sensed any painful urge to void until the intravesical pressure exceeded maximum intraurethral pressure, whereupon CO2 began to escape around the urethroscope. Ten of fifteen patients who had an abnormal rise in pressure during vesical filling were capable of voiding to less than a 50 ml urinary residual. Bladder pressure profiles eventually returned to normal in all subjects. Hypertonic cystometric findings persisted for 14 to 210 days, with a mean of 46 days. No patient redeveloped bladder hy-

To determine whether the parasympathetic nervous system was responsible for detrusor hypertonia, Pro-Banthine was administered to three patients and cystometric evaluation was repeated. In each instance, the

<sup>†</sup>Mean decrease = 32.

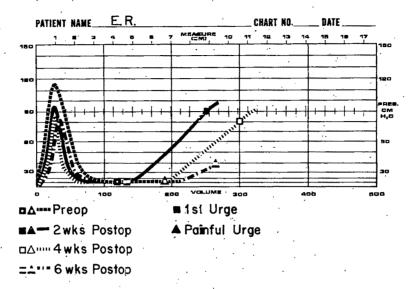


Fig. 3. Preoperative and serial postoperative urethral and vesical pressure studies on patient E. R. Note the postoperative diminution of intrauretaral pressure, the uniformly low initial intravesical pressure, and the progressive rise in intravesical pressure that occurred postoperatively.

Table VI. Bladder pressure profiles at 10 to 14 days postoperatively

Patient	Complete cardinal ligament transection	Patient	Incomplete cardinal ligament transection
D. G.	Normal filling pressure, progressive rise beginning at 200 cc CO <sub>2</sub>	Н. С.	Normal filling pressure, no rise
В. Т.	Normal filling pressure, progressive rise beginning at 110 cc CO <sub>2</sub>	B. E.	Normal filling pressure, no rise
L. L	Normal filling pressure, progressive rise beginning at 110 cc CO <sub>2</sub>	г <b>Ј. С.</b>	Normal filling pressure, no rise
A. D.	Normal filling pressure, progressive rise beginning at 120 cc CO <sub>2</sub>	P. M.	Normal filling pressure, progressive rise beginning at 160 cc CO <sub>2</sub>
E. R.	Normal filling pressure, progressive rise beginning at 125 cc GO <sub>2</sub>	R. N.	Normal filling pressure, no rise
<b>B. P.</b>	Normal filling pressure, progressive rise beginning at 100 cc CO <sub>2</sub>	м. G.	Normal filling pressure, progressive rise beginning at 110 cc CO <sub>2</sub>
W. C.	Normal filling pressure, progressive rise beginning at 130 cc CO <sub>2</sub>	Ņ. H.	Normal filling pressure, no rise
K. M.	Normal filling pressure, progressive rise beginning at 250 cc CO <sub>2</sub>	F. G.	Normal filling pressure, no rise
J. R.	Normal filling pressure, progressive rise beginning at 225 cc GO <sub>2</sub>	D. P.	Normal filling pressure, no rise
R. J.	Normal filling pressure, progressive rise beginning at 150 cc CO <sub>2</sub>	M. S.	Normal filling pressure, progressive rise beginning at 200 cc CO <sub>2</sub>
F. T.	Normal filling pressure, progressive rise beginning at 225 cc CO <sub>2</sub>	L. B.	Normal filling pressure, progressive rise beginning at 130 cc CO <sub>2</sub>

bladder pressure profile was unaffected by this parasympatholytic agent.

Urinary infection. At the time of removal of the suprapubic catheter, the urine culture was positive in only one patient. Six patients had one or two positive postoperative urine cultures. Infection was asymptomatic in four patients, and the other two had symptoms compatible with cystitis. The culture obtained at the most recent postoperative examination in each subject was sterile.

#### Comment

The findings of this study are in agreement with previously described alterations in bladder function that followed radical hysterectomy, e.g., (1) decreased and altered awareness of vesical distention, (2) prolonged postoperative urinary retention, (3) stress incontinence, and (4) hypertonic cystometric findings. In view of these findings and those of other investigators, the etiology as well as the practical significance of these four derangements will be discussed.

Sensory deficit. Autonomic afferent nerves traverse the cardinal, uterosacral, and pubovesicocervical ligaments, and, of necessity, many are transected during the performance of radical hysterectomy. This undoubtedly explains vesical sensory loss after radical hysterectomy. In this study the degree of sensory impairment did not markedly differ between the radical and less radically treated groups of patients. This finding suggests that afferent nerves are concentrated proximally in the cardinal, uterosacral, and pubovesicocervical ligaments, so that leaving the inferior portion of these ligaments adds little to sensory integrity.

With loss of physiologic cortical sensory input, patients should become aware of secondary, less sensitive indicators of vesical distention, such as peritoneal stretching and pressure on adjacent abdominal viscera. The substitute sensations of bloating and vague pelvic heaviness were present in the patients of this study, as well as in patients reported on by other investigators.<sup>3, 7, 8</sup>

Postoperative urinary retention. Normal micturition requires a prolonged, forceful, and coordinated detrusor muscle contraction. Such a contraction is dependent upon a complex interplay of sensory impulses from the bladder, cortical and brain stem modulation of the sacral micturition center, and parasympathetic neurons innervating the bladder detrusor. Since sensory afferent and autonomic efferent nerves are divided at the time of radical hysterectomy, a less than physiologic detrusor contraction that results in the inability to void and a high urinary residual is a predictable, well-recognized, and herein reaffirmed sequel of radical hysterectomy. Using the denervation supersensitivity test of Lapides and associates,14 Glahn7 and Seski and Diokno<sup>10</sup> independently demonstrated parasympathetic denervation in patients who had undergone radical hysterectomy. This test remains positive for months to years after radical hysterectomy, and indicates that regeneration of preganglionic parasympathetic nerves may never occur. Although such regeneration is possible, the likelihood of regrowth across the void created by radical excision of paravaginal tissue seems to be remote.

The present study demonstrates that voiding to low residual occurs sooner in the postoperative period if transection of the cardinal ligaments is incomplete, and I assume that partial transection spares more preganglionic parasympathetic neurons and allows for earlier accommodation of the nervous system and adaptation of the patient to their numerical loss. Although the intent of radical hysterectomy is to obtain a wide cancer-free margin, the inferior segments of the cardinal ligaments are far removed from small cancers confined to the cervix, and because sparing these seg-

ments appears to hasten and facilitate postoperative voiding, the surgeon should consider this operative modification in patients with small, Stage I malignancies.

From a practical standpoint, the knowledge that bladder contractions will be unphysiologic after a complete or partial parasympathetic denervation makes it imperative that the bladder detrusor be functionally normal preoperatively, and that it not be subjected to mechanical injury postoperatively. An exception to this may be in the patient who has an "unstable bladder syndrome." One accepted treatment for this disorder is partial denervation of the bladder, and the single patient in this series who had an "unstable bladder" experienced improvement of the condition as a consequence of radical hysterectomy.

To avoid the mechanical damage to the detrusor muscle that may result from urinary retention, long-term decompression of the bladder is advised. I believe that the intraoperative placement of a suprapubic catheter, combined with instruction of the patient in regard to management of the catheter, offers the best prophylaxis against injury to the bladder muscle, the lowest incidence of urinary infection, and the highest degree of acceptance by the patient.

Few patients after radical hysterectomy rely solely upon a detrusor contraction to empty the bladder. Most patients in this study initiated and completed micturition by using accessory somatic muscles—the rectus and diaphragm. For this reason, before attempted removal of the catheter, all patients should be educated in these mechanisms of voiding and should have sufficient strength and mobility to successfully use them.

Stress incontinence. Five women developed stress incontinence postoperatively, and the problem worsened in one of two patients who had preexisting incontinence. Urethral pressure profile data revealed that in 17 of 22 patients there was a 20 cm H<sub>2</sub>O or greater decrease in maximum intraurethral pressure in the postoperative period. This does not reflect a lack of estrogen, since all women who underwent oophorectomy were given estrogen prophylactically. It has been conjectured that the basis of postoperative stress incontinence is radical resection of the cervix and upper vagina that results in decreased vesical neck support. 1, 3, 4, 6, 7 Such was the urethroscopically demonstrated finding in seven women in this study. However, neurogenic factors may play a role and will be discussed below in conjunction with an explanation of postoperative detrusor hypertonia.

Hypertonic cystometric findings. When cystometry is performed at a time remote from radical hysterectomy, investigators have often discovered that patients have a high-capacity bladder with a low filling pressure

and a large urinary residual.1, 15 It was once assumed that hypotonia was characteristic of the detrusor muscle after radical hysterectomy, and that this finding was entirely due to parasympathetic denervation. Postoperative hypotonia, however, does not fit all investigators' observed cystometric findings after radical hysterectomy. Those who have performed serial cystometry, beginning in the period immediately after radical hysterectomy, have discovered that the bladder had a high filling pressure and a reduced capacity.75 10, 16, 17 With the passage of time, the filling pressure returned to normal, and only those patients who had histories compatible with overdistention developed a hypotonic cystometrogram. Serial cystometric data on the patients presented herein corroborate both findings, i.e., hypertonus proximal to the operative site and hypotonia with chronic vesical overdistention.

There have been two explanations for the detrusor hypertonia observed immediately after operation: (1) parasympathetic dominance, 17, 18 and (2) a decrease in the musculoelastic properties of the detrusor muscle and the paravesical soft tissue as a consequence of postoperative edema, hematoma, and cicatricial changes. 7, 10 This study and that of Seski and Diokno<sup>10</sup> suggest that the first theory is improbable because detrusor hypertonia is not abolished by parasympatholytic drugs. The second theory, favored by Glahn<sup>7</sup> and Seski and Diokno, 10 fails to explain why many, but not all, patients in this study had a hypertonic cystometrogram postoperatively. It is also striking that subjects who had a complete division of the cardinal ligaments had a 100% incidence of hypertonia, as compared to 30% in the group which underwent the less radical operation.

The findings in this study and a rewview of currently held theories in regard to vesical neurophysiology lead me to propose sympathetic denervation as an alternate reason for postoperative detrusor hypertonia. Previous explanations for all aspects of bladder dysfunction after radical hysterectomy have been based upon the assumption that transection of sympathic autonomic nerves, which also traverse the cardinal, uterosacral, and pubovesicocervical ligaments, is without physiologic significance.2, 7, 9, 10 However, in view of studies which show a highly important functional role for the sympathetic nervous system in the physiology of vesical filling, 19-25 it seems unlikely that the division of a major portion of the vesical sympathetic nerve supply could be inconsequential. The bladder detrusor and vesical neck are richly endowed with sympathetic nerves, and it has been unequivocally demonstrated that the bladder and upper urethra are under dual sympathetic and parasympathetic innervation. Additionally, many short, intrinsic neurons interconnect these two divisions of the autonomic nervous system. These interconnections occur at the level of parasympathetic ganglia and depress parasympathetic conduction, thus favoring continence during vesical filling.26 It is also recognized that sympathetic postganglionic nerves terminate upon both alpha and beta adrenoreceptors, and that alpha and beta receptors are distributed unevenly throughout the detrusor muscle, vesical neck, and urethra.27-29 When stimulated, the beta-adrenergic receptors which are diffusely present throughout the bladder muscle cause relaxation of the detrusor muscle, and the alpha-adrenergic receptors which are concentrated in the vesical neck and upper urethra cause contraction of smooth muscle.

On the basis of studies which suggest that, under normal conditions, vesical filling without a rise in pressure is partly due to sympathetic beta-adrenergic stimulation, 29, 30 and not solely to the intrinsic properties of the detrusor muscle and perivesical connective tissue bed,31 I postulate that sympathetic denervation contributes to bladder hypertonus after radical hysterectomy. Additionally, I postulate that the loss of alpha stimulation to the vesical neck partially explains the postoperative decrease in intraurethral pressure and contributes to the observed incidence of postoperative stress incontinence.

This hypothesis is compatible with the observed cystometric findings. It is also compatible with the lower incidence of vesical hypertonia which occurred in patients who had incomplete transection of the cardinal ligaments. The return to a normal bladder pressure profile did not occur in some patients until several months after radical hysterectomy, and an explanation of hypertonus based solely upon perivesical edema and hematoma formation could not explain this duration of hypertonic change. However, regeneration of injured nerves and autonomic adaptation could explain temporary hypertonia, with ultimate return to normal. To test this hypothesis in future studies, I plan to measure the effect of sympathomimetic and sympatholytic agents on postoperative urethral and vesical tone.

#### REFERENCES

- 1. Thornton, W. N., Jr.: Late urinary system complications following radical hysterectomy for carcinoma of the cervix, Am. J. Obstet. Gynecol. 67:867, 1954.
- 2. Twombly, G. H., and Landers, D.: The innervation of the bladder with reference to radical hysterectomy, Am. J. OBSTET. GYNECOL. 71:1291, 1956.
- Lewington, W.: Disturbances of micturition following

- Wertheim hysterectomy, J. Obstet. Gynaecol. Br. 63:861, 1956.
- Green, T. H., Jr., Meigs, J. V., Ulfelder, H., et al.: Urologic complications of radical Wertheim hysterectomy: Incidence, etiology, management, and prevention, Obstet. Gynecol. 20:293, 1962.
- Symmonds, R. E.: Morbidity and complications of radical hysterectomy with pelvic lymph node dissection, Am. J. OBSTET. GYNECOL. 94:663, 1966.
- Fraser, A. C.: The late effects of Wertheim's hysterectomy on the urinary tract, J. Obstet. Gynaecol. Br. Commonw. 73:1002, 1966.
- Glahn, B. E.: The neurogenic factor in vesical dysfunction following radical hysterectomy for carcinoma of the cervix, Scand. J. Urol. Nephrol. 4:107, 1970.
- 8. Palm, L., and Folke, R.: Bladder function following either radiotherapy or radical operation ad modum Okabayashi for cervical cancer, Dan. Med. Bull. 17:113, 1970.
- Barclay, D. L., and Roman-Lopez, J. J.: Bladder dysfunction after Schauta hysterectomy, Am. J. OBSTET. GYNE-COL. 123:519, 1975.
- Seski, J. C., and Diokno, A. C.: Bladder dysfunction after radical abdominal hysterectomy, Am. J. Obstet. Gynecol. 128:643, 1977.
- Meigs, J. V.: Radical hysterectomy with bilateral dissection of the pelvic lymph nodes.
   The method of Joe V. Meigs, M.D., in Meigs, J. V., editor: Surgical treatment of cancer of the cervix, New York, 1954, Grune & Stratton, Inc., pp. 149-196.
- 12. Robertson, J. R.: Gas cystometrogram with urethral pressure profile, Obstet. Gynecol. 44:72, 1974.
- 13. Smith, P. H., and Ballantyne, B.: The neuroanatomical basis for denervation of the urinary bladder following major pelvic surgery, Br. J. Surg. 55:62, 1968.
- Lapides, J., Friend, C. R., Ajemian, E. P., et al.: Denervation supersensitivity as a test for neurogenic bladder, Surg. Gynecol. Obstet. 114:241, 1962.
- Fraser, A. C.: Cystometry after Wertheim's hysterectomy,
   J. Obstet. Gynaecol. Br. Commonw. 74:746, 1967.
- Richter, K., and Albrich, W.: Zur Frage der postoperativen Harnverhaltung nach erweiterter total extirpation wegen carcinoma colli uteri, Zbl. Gynäkol. 73:1103, 1951.
- Roman-Lopez, J. J. and Barclay, D. L.: Bladder dysfunction following Schauta hysterectomy, Am. J. Obstet. Gynecol. 115:81, 1973.

- 18. Yousseff, A. F.: Cystometric studies in gynecology and obstetrics, Obstet. Gynecol. 8:81, 1956.
- El-Badawi, A.; and Schenk, E. A.: Dual innervation of the mammalian urinary bladder. A histochemical study of the distribution of cholinergic and adrenergic nerves, Am. J. Anat. 119:405, 1966.
- 20. El-Badawi, A., and Schenk, E. A.: A new theory of the innervation of bladder musculature. Part I. Morphology of the intrinsic vesical innervation apparatus, J. Urol. 99:585, 1968.
- 21. Boyarsky, S., Labay, P., Gregg, R., et al.: Pharmacologic studies of the nature of the sympathetic nerves of the urinary bladder, Paraplegia 5:136, 1968.
- Malin, J. M., Jr., and Boyarsky, S.: The effects of cholinergic and adrene-gic drug stimulation of detrusor muscle, Invest. Urol. 8:286, 1970.
- 23. El-Badawi, A., and Schenk, E. A.: A new theory of the innervation of bladder musculature. Part 4. Innervation of the vesicourethral junction and external urethral sphincter, J. Urol. 111:613, 1974.
- 24. Bradley, W. E., and Timm, G. W.: Physiology of micturition, Vet. Clin. North Am. 4:487, 1974.
- Khanna, O. P.: Disorders of micturition. Neuropharmacologic basis and results of crug therapy, Urology 8:316, 1976.
- Ostergard, D. R.: The neurological control of micturition and integral voiding reflexes, Obstet. Gynecol. Surv. 34:417, 1979.
- 27. Edvardsen, P., and Sezekleiv, J.: Distribution of adrenergic receptors in the urinary bladder of cats, rabbits and guinea pigs, Acta Pharmacol. Toxicol. 26:437, 1968.
- 28. Gregg, R. A., Boyarsky, S., Labay, P., et al.: Presence of beta-adrenergic receptors in urinary bladder of dog and cat: Response to isoproterenol, Arch. Phys. Med. Rehabil.
- Nergardh, A.: Autonomic receptor functions in lower urinary tract. Survey of recent experimental results, J. Urol. 113:180, 1975.
- Rohner, T. J., Raezer, D. M., Weiss, A. J., et al.: Contractile responses of dog bladder neck muscle to adrenergic drugs. J. Urol. 105:657, 1971.
- drugs, J. Urol. 105:657, 1971.
  31. Tang, P. C., and Ruch, T. C., Non-neurogenic basis of bladder tonus, Am. J. Physiol. 181:249, 1955.

Temporal relationships between ovulation and defined changes in the concentration of plasma estradiol- $17\beta$ , luteinizing hormone, follicle-stimulating hormone, and progesterone

#### I. Probit analysis

World Health Organization, Task Force on Methods for the Determination of the Fertile Period, Special Programme of Research, Development and Research Training in Human Reproduction\*

One hundred seventy-seven women have been studied over the periovulatory period, in order to obtain detailed information on temporal relationships between ovulation and defined changes in the concentrations of estradiol-17 $\beta$  (E<sub>2</sub>), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and progesterone (P) in peripheral plasma. Serial samples of blood were taken, the surfaces of the ovaries were examined at laparotomy, and the mature follicle or corpus luteum was removed for histologic examination. The results in 107 cases fulfilled the criteria for statistical analysis, and in 78 the operation was performed after the follicle had ruptured. A probit analysis was undertaken with use of the proportion of women who had ovulated at a given time in relation to the interval from a defined rise or peak in the concentration of a circulating hormone. The median time intervals (in hours) from the hormonal event to ovulation and the 95% confidence limits of the estimates are as follows:  $17\beta$ -estradiol—rise 82.5 (54.0 to 100.5), peak 24.0 (16.9 to 32.1); LH—rise 32.0 (23.6 to 38.2), peak 16.5 (9.5 to 23.0); FSH—rise 21.1 (14.1 to 30.9), peak 15:3 (8.1 to 21.7); progesterone—rise 7.8 (-12.5 to 15.3). From the statistical model for LH it was possible to estimate that ovulation in 90% of the cases had occurred between 16 ( $\pm$ 6) and 48 ( $\pm$ 6) hours after the first significant rise in the concentration of this hormone and between -3 ( $\pm 5$ ) and 36 ( $\pm 5$ ) hours after the peak. An examination of the individual results in every woman gave corresponding ranges of between 24 and 56 hours from the first significant rise in LH and between 8 and 40 hours after the peak. From a practical standpoint, the conclusion is that a defined rise in the concentration of circulating LH is the best indirect parameter of impending ovulation. (AM. J. OBSTET. GYNECOL. 138:383, 1980.)

THERE IS STILL a need for the development of simple, reliable methods to predict or detect ovulation in women. The availability of such techniques would help to establish new and improved methods of family planning and also aid the treatment of infertile couples. To date, the only direct method involves the isolation of a secondary oocyte from the reproductive tract. <sup>1–3</sup> This approach is technically difficult and im-

Received for publication November 9, 1979. Accepted June 18, 1980.

Reprint requests: J. Spieler, Special Programme of Research in Human Reproduction, World Health Organization, 1211 Geneva 27. Switzerland.

\*Task Force investigators in this study and their affiliations are given at the end of the article.

practicable on a routine basis. Consequently, most emphasis has been placed on the development of indirect approaches. These are based upon the observation that ovulation is associated with marked changes in the secretion of ovarian hormones, which, in turn, produce specific responses in those tissues that are sensitive to the level of circulating steroids.

Before simple techniques can be assessed with confidence, it is necessary to obtain more detailed information on the temporal relationships between the concentration of hormones in peripheral venous plasma, ovarian morphologic features, and the occurrence of ovulation in the same group of women. In the past, these parameters have usually been studied independently. Thus, Corner<sup>4</sup> described in detail changes in the morphologic features of the postovulatory folli-

384 WHO Task Force October 15, 1980
Am. J. Obstet. Gynecol.

cle or corpus luteum. Subsequently, studies with the use of radioactive tracers and immunoassay techniques demonstrated that there are characteristic changes in the concentration of plasma gonadotropins and steroid hormones during the ovarian cycle.<sup>5–11</sup> At the same time, other experiments established their source, metabolic clearance rates, and uptake by responsive tissues.<sup>12</sup>

To date, there have been four studies on the relationship between the levels of circulating hormones and the time of ovulation as estimated by histologic dating of the corpus luteum. The first group of workers13, 14 determined the concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and progesterone (P) in 8-hour samples of peripheral plasma from five subjects over the mid-cycle period and found that ovulation probably occurred 24 to 36 hours after the initial rise in LH or 12 to 24 hours after the peak level. The second group, in a preliminary report,15 localized ovulation at about 40 hours after the initiation of the LH surge, and then, after a more detailed study of seven ovulatory women, revised the estimated time interval to 36 hours. 16 Subsequently, the results from a detailed study of 17 healthy women showed that ovulation could occur within 15.5 hours after the LH peak, but might not take place until more than 54 hours after that hormonal event.<sup>17</sup> Finally, Pauerstein and associates<sup>18</sup> studied 23 subjects and concluded that the mean time from the LH peak to ovulation was 9 hours.

The purpose of the present investigation was to extend these observations by studying a large number of women who were scheduled for laparotomy for reasons other than ovarian dysfunction. The principal aims were to relate defined changes in the concentration of  $17\beta$ -estradiol (E<sub>2</sub>), LH, FSH, and progesterone in peripheral plasma to the process of ovulation. The method involved making a definitive judgment as to whether ovulation had occurred at the time of operation and the use of probit analysis19 to estimate the median time intervals. This technique uses results from both preovulatory and postovulatory cases and is independent of histologic dating. It was hoped that the information from a new approach and a relatively large number of women would provide a well-defined reference method for the prediction or detection of ovulation and thereby help in the evaluation of novel and simpler techniques.

#### Material and methods

A protocol was written for a multicenter collaborative study. Each of 10 centers was to study at least 20 women and provide the following information: the concentrations of E<sub>2</sub>, FSH, LH, and P in serial samples of peripheral plasma or serum; a description (with photographic documentation) of the surface morphologic features of both ovaries at laparotomy; an excision biopsy specimen of the mature follicle or early corpus luteum; and a definitive statement by the surgeon as to whether ovulation had occurred.

Subjects. The following criteria had to be fulfilled before a patient was admitted into the study: The patient had to be between 21 and 40 years old, inclusive. There had to be a medical reason, other than the purpose of the study, for laparotomy. There could be no evidence or history of endocrine or other diseases which might influence the menstrual cycle or impede visual observation of the ovaries (e.g., thyroid disease, extensive pelvic infection, ovarian tumors). There had to be clear, recorded, clinical evidence that the patient had had regular, spontaneous menstrual cycles of 25 to 32 days in length for the three cycles immediately preceding the study. No oral contraceptives were to have been used over this period, and long-acting hormonal preparations were to have been excluded for the preceding 6 months. For the purposes of this study, documentation of regular ovulatory cycles included evidence of luteal function as indicated by the concentrations of plasma progesterone, urinary pregnanediol, or histologic features of the endometrium. Furthermore, it was recommended that the parameters chosen should be related to the shift in basal body temperature (BBT) and the onset of the next menstrual period. The erythrocyte, leukocyte and differential blood counts, hemoglobin concentration, and hematocrit had to be within the normal range for the population being studied. No hormonal contraceptives were to have been taken during the cycle when operation was scheduled to take place.

The aims and procedure were explained in detail to every patient. Only those who consented freely to participate were finally admitted into the study. All volunteers understood that they were free to withdraw from the investigation at any time.

Design. For practical reasons, it was necessary to estimate the expected day of ovulation (EDO) and then plan the times for sampling of blood, admission to the hospital, and operation. This design feature ensured that the operation occurred before follicular rupture in some cases and after it in others—as required to achieve the objectives of the study. The EDO was generally taken as the (L-13) day of a cycle, in which L was the mean length of the last three menstrual cycles. The first day of menstrual bleeding was taken as the first day of the cycle. The operative procedure (Day 0) was provisionally scheduled for the EDO. In practice, the

time of operation was often adjusted according to clinical judgment, the results from rapid hormone assays, or the availability of local facilities.

A sample of blood was taken at the same time every morning from Days -8 to -4 and after the operation on Days +3 and +10. The frequency of sampling was increased (three samples per day, usually at 0800, 1600 and 2400 hours) for the period from three days before to two days after the operation. In general, the information derived from samples of blood removed after operation was used only to confirm that the main steroid-producing structure had been removed for histologic examination. Occasionally, the values for LH and FSH for up to 32 hours after the operation were used to confirm the presence of an initial rise in or peak for these hormones. The volume of blood per sample did not exceed 10 ml-thus, less than 250 ml per subject was taken throughout the entire study.

Hormone assays. The concentrations of E<sub>2</sub>, LH, FSH, and P were measured in duplicate by radioimmunoassay of plasma or serum. For each hormone, all samples from a single subject were measured in the same assay. The values for LH and FSH were reported as mIU/ml, for E<sub>2</sub> as pg/ml, and for P as ng/ml. All centers participated in a World Health Organization (WHO) international quality control scheme for the measurement of these hormones, and their performance was closely monitored during the period of this

Morphologic study of surface of ovaries. The record for every case included the following information: the date and time of day when the observations were made; the greatest length, width, and thickness of each ovary measured in centimeters; a complete description of the morphologic features of the ovarian surfaces, including the number of large (ruptured or unruptured) follicles; color photographs of the anterior and posterior surfaces of the two ovaries against a centimeter scale; a statement by the surgeon as to whether ovulation had occurred; details of the operating procedure; the site from which the biopsy specimen was removed (drawn on a form provided by WHO).

Biopsy of ovary. The growing or hemorrhagic follicle or corpus luteum was identified and excised according to the following procedures: Preovulatory follicles, follicular fluid was aspirated and the follicle was excised together with some adjacent ovarian tissue; large follicles were cut into sections 3 to 5 mm in width. Corpora lutea, every corpus luteum was excised by a wedge resection (anterior face to posterior face) and cut into slices 3 to 5 mm thick.

All tissues were fixed in Bouin's solution and embedded in paraffin wax. The specimens were sectioned, stained with hematoxylin and eosin, and examined under the light microscope by the pathologist (M. Maqueo), who prepared a report without any additional information except the identifying numbers of

All information relevant to the study was recorded on standard forms provided by WHO and dispatched to Geneva for data processing.

Definitions. The results from all centers were reviewed by a committee, which consisted of a clinician, biochemist, histologist, statistician, and a member of the WHO secretariat. Criteria for excluding entire cases were agreed upon (Table I). In addition, the following definitions were formulated for certifying ovulation and identifying changes in plasma hormone conœntrations.

Certified ovulation. Whether ovulation had or had not occurred was assessed initially at laparotomy by the operating surgeon. His clinical impressions were documented by color photographs showing ovarian morphologic features. The opinion of the histologist served to confirm or deny the surgeon's assessment. A preovulatory follicle was defined 20 as having a prominent theca layer with a well-developed vasculature. The theca cells were large with prominent nuclei and nucleoli. The membrana granulosa consisted of several cell layers. Cells close to the basement membrane were large and possessed a moderate amount of cytoplasm and medium-sized nuclei. Cells closer to the antrum were smaller with less cytoplasm. Mitoses of the granulosa cells were rare or absent. No capillaries or blood cells were seen between the granulosa cells. An early postovulatory follicle (or corpus luteum) was defined according to the criteria of Corner.4 The theca layer was disorganized; the cells were smaller and their nuclei more dense. Capillaries were large and engorged, and hemorrhagic patches were often seen. The membrana granulosa was disorganized and its cells were dissociated, with many lying freely in the follicular cavity. Their cytoplasm was faintly eosinophilic, and the nuclei were medium sized. Hemorrhagic patches were seen among the granulosa cells.

A categorical statement (Yes or No) on the occurrenze of ovulation before operation was made only if there was agreement between the surgeon and the histologist.

First significant rise in circulating hormone. The first significant rise in circulating hormones was the first value that was 1.5 times the mean of the preceding baseline values. For E2, LH, and FSH, the first significant rise also led to the peak, without an intermediary decrease.

Peak. The peak was the highest value that was pre-

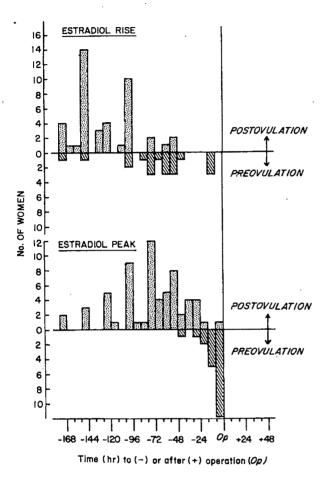


Fig. 1. The distribution of time intervals from the first significant rise and peak of plasma estradiol to the time of operation (Op) and the occurrence of ovulation.

ceded and followed by lower values, and was at least three times the preceding mean baseline value for LH or twice the corresponding values for FSH and E<sub>2</sub>. When there were two peak values of identical magnitude, the first was chosen.

**Statistical analysis.** The statistical technique of probit analysis<sup>19</sup> was used to estimate median intervals between the defined changes in plasma hormone concentrations and ovulation.

This approach has been used primarily in biologic assay work to estimate the dose required to produce a given qualitative response (e.g., death or survival) in half of a group of experimental animals. The basic information required is the proportion which shows this response at different doses. When a normal cumulative distribution curve is fitted to these data, the dose required to produce a response in 50% of the animals, e.g. the "LD 50," can be estimated with stated precision, expressed in terms of the usual confidence (or fiducial) limits.

Table I. Exclusion criteria

Reason	No. excluded
Ovarian abnormalities	
Presence of atretic follicles only; anovulatory cycles	27
Endometriosis ·	3
Cystadenoma Protocol violation	1
Gross mistiming of operation	5
Insufficient results on hormone levels	4
Incorrect biopsy sampling	2
Ambiguity over dates (between first day of blood sampling and day of operation)	2
Incorrectly labeled specimens or doubtful assay results	11
Irreconcilable discrepancies between hormonal, clinical, and histologic parameters	15
Total	70

This technique was applied to the data of this study by replacing dose with the time from a given hormonal event to operation. The response was ovulation or no ovulation at operation. The women were then grouped by intervals of 8 hours from the hormonal event to operation. The proportion of women who were found to have ovulated among those who were operated on within 8 hours after the hormonal event was calculated as well as the corresponding proportion among those who were operated on between 8 and 16 hours after the hormonal event, between 16 and 24 hours, and so forth. Proportions were also calculated for the women operated on in the 8 hours before the hormonal event, and between 8 and 16 hours before the event. A series of increasing percentages (response rates) from 0 to 100 was obtained, starting at a time before any woman had ovulated and ending after all women had ovulated. From this information the time at which 50% had ovulated was estimated. Confidence intervals can be associated with this estimate of the median time interval in much the same way as they are used to express the degree of precision of a mean. The width of the confidence interval will depend on the size of the sample and the spread of the times between the hormonal event and ovulation, i.e., the biologic variability of the parameter. The smaller the biologic variation and the larger the sample, the greater the precision will be (i.e., the narrower the confidence interval).

An important point is that this technique makes use only of the information about whether a woman has or has not ovulated before operation and is not dependent on histologic dating of the corpus luteum. It also makes use of information about women who have not ovulated at operation, as well as about those who have. On the other hand, the method depends on the fit of the values to a normal distribution curve. When this

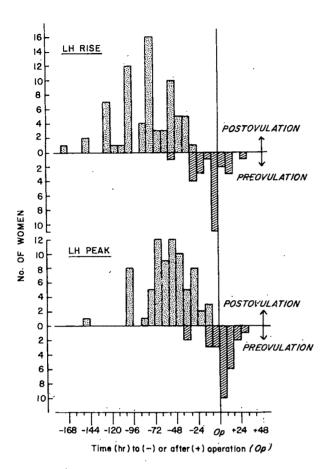


Fig. 2. The distribution of time intervals from the first significant rise and peak of plasma LH to the time of operation (Op) and the occurrence of ovulation.

aspect was tested, there was no statistically significant departure from a good fit in any of the data presented here. Another possible curve, that of the log-normal distribution, is often applicable to biologic data. This was also tested and fitted equally well, and it gave very similar results.

It is also possible to estimate from the same model not only the times after a hormonal event at which 50% of the women will have ovulated, but the times at which any other percentage of them will have ovulatedagain on the assumption that the data are fitted by a normal distribution or by a log-normal distribution. In particular, the times at which 5% and 95% will have ovulated were estimated, giving, therefore, an estimate of the interval within which 90% of ovulations occur and, hence, of the biologic variability; this estimate should not be confused with the confidence interval of the median, which is merely a statement of precision. The estimate of the times at which 5% and 95% will . have ovulated also cannot be precise. For convenience of presentation in the table concerned, standard errors

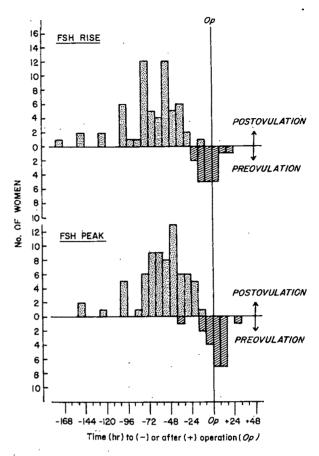


Fig. 3. The distribution of time intervals from the first significant rise and peak of plasma FSH to the time of operation (Op) and the occurrence of ovulation.

rather than confidence intervals have been used to express the degree of precision of these estimates.

#### Résults

One hundred seventy-seven cases were studied; of these, 107 provided results for analysis, although defined rises and peaks could not always be identified for all four hormones because of the amount of baseline information available. The number of cases excluded for various reasons is shown in Table I. The group headed "irreconcilable discrepancies" between parameters includes cases in which the surgeon and histologist disagreed as to whether ovulation had occurred.

Ovulation had not occurred at the time of operation in 29 of the acceptable cases, whereas 78 contained a corpus luteum.

Distribution of values. The distribution of time intervals (in groups of 8 hours) from the hormonal event to operation is shown in a histogram for each hormone in Figs. 1 through 4. The number of subjects is also

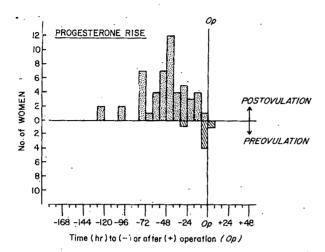


Fig. 4. The distribution of time intervals from the first significant rise of plasma progesterone to the time of operation (Op) and the occurrence of ovulation.

**Table II.** Range of observed times from defined hormonal events within which ovulation occurs

	Time of ovulation (hr) from:			
Hormone	First significant rise	Peak.		
17β-estradiol	48 to 168	0 to 48		
LH	24 to 56	8 to 40		
FSH	8 to 24	8 to 40		
Progesterone	0 to 32	_		

plotted relative to whether ovulation had or had not occurred before the operation. The times from each of the hormonal events within which ovulation occurred are shown in Table II.

Probit estimates. The median intervals and 95% confidence limits from the first significant rises in  $\mathbb{E}_2$ , LH, FSH, and P to ovulation are shown in Table III. The first significant rise in  $\mathbb{E}_2$  usually occurred during the period of daily sampling of blood, and the distribution of time intervals from this hormonal event to ovulation was so wide (see Fig. 1) that the proportions of women who had ovulated at operation were calculated over periods of 24 hours. The time intervals from the respective peak values to ovulation are shown in Table IV. An estimate of the range of values within which 90% of the individual observations could be expected to lie, together with the standard errors of the estimates, is given in Table V.

#### Comment

The results from this study have enabled us to calculate with reasonable confidence the temporal relationships between ovulation and defined changes in the concentration of plasma gonadotropins and ovarian

**Table III.** Time intervals between first significant rises in the concentration of circulating hormones and ovulation

	No. of obser-	Median interval	Confidence limits of estimates		
Hormone	vations	(hr)	Lower 95%	Upper 95%	
17β-Estradiol*	64	82.5	54.0	100.5	
LĤ	97	32.0	23.6	38.2	
FSH .	79	21.1	14.1	30.9	
Progesterone	58	7.8	-12.5	15.9	

<sup>\*</sup>Because of the number of observations and the distribution of time intervals, 24-hour intervals were used for these estimates (see Fig. 1).

**Table IV.** Time intervals between peak levels of circulating hormones and ovulation

	No. of obser-	Median interval	Confidence limits of estimates		
Hormone vations	(hr)	Lower 95%	Upper 95%		
17β-estradiol	84	24.0	16.9	32:1	
LH	103	16.5	9.5	23.0	
FSH	94	15.3	8.1	21.7	

**Table V.** Estimated times (by probit analysis) within which 90% of ovulations occur from defined hormonal events

	First significant rise		Peak	
Hormone	Range (hr)	SE	Range (hr)	SE
17β-estradiol	*5 to 160	±22	3 to 45	±6
LH	16 to 48	±6	-3 to 36	$\pm 5$
FSH	9 to 33	$\pm 12$	0 to 31	$\pm 5$
Progesterone	-12 to 27	±10	·	

<sup>\*</sup>Estimates based on 24-hour intervals (see Table III).

steroids. However, there were some difficulties associated with the interpretation of results. For example, it was difficult to identify the first significant rises and peak values for some plasma hormones—particularly FSH. This problem was related to the time between ovulation and operation and, hence, to the amount of baseline information that was available. The frequency of sampling prior to the third day before operation also imposed some limitations; thus, the initial rise in plasma FSH often coincided with the peak value. To deal with these difficulties a committee was convened to review the results. Definitions were agreed upon and every case was assigned to an appropriate category. The reference points and time intervals for probit analysis were determined and decisions were made, about which results should be included in the analyses.

Perhaps the most encouraging feature of the final results was the limited biologic variation. Consequently, it appears possible to use a hormonal parameter (LH rise or peak) to predict that ovulation will occur within a defined period of 32 hours (24 to 56 hours after rise; 8 to 40 hours after peak). It is also reassuring that estimates of the median times from defined hormonal events to ovulation give values similar to those previously determined by means of the method of histologic dating. 13-18 Moreover, both the model of a normal and that of a log-normal distribution of individual values fitted the data.

The median time interval from the first significant rise in E2 to ovulation was 82.5 hours, but the confidence limits associated with this estimate were relatively wide (see Table III and Fig. 1). This finding raises the question of whether this rise in E2 will invariably precede the start of the fertile period, which may occur at least 72 hours before ovulation because of the fertilizing life span of sperm in the female reproductive tract. This limitation, however, may have arisen from the applied definition of a rise in the present study, the frequency of sampling, and the fact that blood was never taken before Day 7 of the menstrual cycle. Accordingly, more studies are required in order to define in more detail the relationship between the initial rise in estradiol and ovulation.

The median time interval from the initial rise in plasma LH to ovulation was 32 hours; this value is similar to that reported by Steptoe and Edwards<sup>2</sup> after the intramuscular injection of human chorionic gonadotropin (hCG) and the results from histologic dating of the corpus luteum. 14, 16 Furthermore, the median time interval from the peak of circulating LH (16.5 hours) is similar to that reported by Yussman and associates14 and Croxatto and associates, 17 but approximately twice that reported by Pauerstein and associates. 18 all of whom used the technique of histologic dating of the corpus luteum. The limitations of that approach, however, have already been discussed, 18 and the application of that method to the present study is the subject of a separate publication. The interval between median times for the first significant rise and the peak of LH was 15.5 hours (see Tables III and IV), and we concluded that either a defined rise in the concentration of circulating LH (greater than that due to pulsatile release) or the peak value are the best hormonal predictors of ovulation. Further analysis of the results from the statistical model indicated that ovulation may occur within 16 hours of the first significant rise in plasma LH, or any time up to 48 hours later, with a standard' error of  $\pm 6$  hours. The corresponding range of values from an examination of the time interval of individual

subjects was from 24 to 56 hours (see Fig. 2). Similarly; the range of intervals from the peak of LH to ovulation by the probit model was -3 to 36 hours, with a standard error of ±5 hours, whereas the individual values gave a range of 8 to 40 hours. It is of interest that the initial rise and peak of FSH tended to occur after those of LH and were more difficult to identify.

It was also found that the interval between the peak concentration of plasma LH and the rise in circulating progesterone was variable, which suggests that functional luteinization of the theca and granulosa cells may precede or follow ovulation. This conclusion is derived from the results of probit analysis, which gave a median value of 7.8 hours from the first significant rise in progesterone to ovulation, but with wide fiducial limits (-12.5 to 15.9). Accordingly, although follicular rupture and biochemical luteinization both follow an increase in the level of circulating LH, a defined change in the concentration of progesterone may only be used to detect, but not predict, the time of ovulation.

Thus, the results from this study are consistent with the hypotheses that the first significant rise in the concentration of estradiol in the peripheral circulation (1.5 times the mean baseline value) may signal a potentially fertile cycle, and that the corresponding rise in plasma LH indicates that ovulation is likely to occur within a well-defined time. From a practical point of view, it is easier to develop a method to determine a defined rise in the concentration of a hormone than a peak value, since at least one extra sample must be taken and analyzed to determine the latter. Identification of the first significant rise in plasma LH by a rapid radioreceptor assay has been shown to be of value in predicting ovulation and monitoring the treatment of infertile women.21

Task Force investigators in this study and their institutions are as follows: S. P. Boyers, Harbor-University of California, Los Angeles, Medical Center, Torrance, California; L. Carenza, Universita di Roma, Rome, Italy; W. P. Collins, King's College Hospital Medical School, London, England; S. Cheviakoff, Universidad Catolica de Chile, Santiago, Chile; J. Ferin, University of Louvain, Louvain, Belgium; P. R. Figueroa-Casas, Grupo de Estudio en Fertilidad y Endocrinologia de Rosario, Rosario, Argentina; C. Gual, Instituto Nacional de la Nutricion, Mexico City, Mexico; J. A. Heady, Department of Clinical Epidemiology and Social Medicine, The Royal Free Hospital School of Medicine, London, England; B. Lunen-Feld, Chaim Sheba Medical Centre, Tel-Hashomer, Israel; M. Maqueo, Hospital de Gineco Obstetricia, Mexico City, Mexico; J. Newton, King's College Hospital Medical School, London, England; S. S. Ratnam, Kandang Kerbau Hospital for Women, University of Singapore, Singapore; J. Spieler, Special Programme of Research in Human Reproduction, World Health Organization, Geneva, Switzerland; G. Stakemann, Hvidovre, Copenhagen, Denmark.

We would like to thank Dr. R. Borth, Dr. G. Benagiano, and Dr. C. A. Woolever for their assistance in the preparation of the original protocol; and the asso-

ciated principal investigators, surgeons, and technicians who participated in the study at each of the institutions. The program for probit analysis was written by Mr. H. Dixon, World Health Organization, Geneva, Switzerland, and the manuscript was typed by Mrs. J. J. McKenzie, London, England.

#### REFERENCES

- Noyes, R. W., Clewe, T. H., Bonney, W. A., Burrus, S. B., De Feo, V. J., and Morgenstern, L. L.: Searches for ova in the human uterus and tubes. I. Review, clinical methodology, and summary of findings, Am. J. OBSTET. GY-NECOL. 96:157, 1966.
- Steptoe, P. C., and Edwards, R. G.: Laparoscopic recovery of preovulatory oocytes after priming the ovaries with gonadotrophins, Lancet 1:683, 1970.
- Člewe, T. H., Morgenstern, L. L., Noyes, R. W., Bonney, W. A., Jr., Burrus, S. B., and De Feo, V. J.: Searches for ova in the human uterus and tubes. II. Clinical and laboratory data on nine successful searches for human ova, Am. J. Obstet. Gynecol. 109:313, 1971.
- 4. Corner, G. W.: The histologic dating of the human corpus luteum of menstruation, Am. J. Anat. 98:377, 1956.
- Ross, G. T., Cargille, C. M., Lipsett, M. B., Rayford, P. L., Marshall, J. R., Strott, C. A., and Rodbard, D.: Pituitary and gonadal hormones in women during spontaneous and induced ovulatory cycles, Recent Prog. Horm. Res. 26:1, 1970.
- Vande Wiele, R. L., Bogumil, J., Dyrenfurth, I., Ferin. M., Jewelewizc, R., Warren, M., Rizkallah, T., and Michael, G.: Mechanisms regulating the menstrual cycle in women. Recent Prog. Horm. Res. 26:63, 1970.
- in women, Recent Prog. Horm. Res. 26:63, 1970.

  7. Abraham, G. E., Odell, W. D., Swerdloff, R. S., and Hopper, K.: Simultaneous radioimmunoassay of FSH, LH, progesterone, 17-hydroxyprogesterone and estradiol-178 during the menstrual cycle, J. Clin. Endocrinol. Metab. 34:312, 1972.
- 8. Guerrero, R., Aso, T., Brenner, P. F., Cekan, S. Z., Landgren, B-M., Hagenfeldt, K., and Diczfalusy, E.: Studies on the pattern of circulating steroids in the normal menstrual cycle. 1. Simultaneous assays of progesterone, pregnenolone, dehydro-epiandrosterone, testosterone, dihydrotestosterone, androstenedione, oestradiol and oestrone, Acta Endocrinol. (Copenh.) 81:133, 1976.
- Aedo, A-R., Landgren, B-M., Cekan, S. Z., and Diczfalusy, E.: Studies on the pattern of circulating steroids in the normal menstrual cycle. 2. Levels of 20α-dihydroprogesterone, 17-hydroxyprogesterone and the assessment of their value in ovulation prediction, Acta Endocrinol. (Copenh.) 82:600, 1976.
- Aedo, A-R., Nunez, M., Landgren, B-M., Cekan, S. L., and Diczfalusy, E.: Studies on the pattern of circulating

- steroids in the normal menstrual cycle. 3. Circadian variation in the periovulatory period, Acta Endocrinol. (Copenh.) 84:320, 1977.
- 11. Landgren, B-M., Aedo, A-R., Nunez, M., Cekan, S. Z., and Diczfalusy, E.: Studies on the pattern of circulating steroids in the normal menstrual cycle. 4. Periovulatory changes in relation to the LH-surge, Acta Endocrinol. (Copenh.) 84:620, 1977.
- 12. Loraine, J. A., and Bell, E. T.: Hormoen assays and their clinical application, ed. 4, Edinburgh, 1976, Churchill Livingstone.
- Yussman, M. A., and Taymor, M. L.: Serum levels of follicle-stimulating hormone and luteinizing hormone and of plasma progesterone related to ovulation by corpus luteum biopsy, J. Clin. Endocrinol. Metab. 30:396, 1970.
- 14. Yussman, M. A., Taymor, M. L., Miyata, J., and Pheteplace, C.: Serum levels of follicle-stimulating hormone, luteinizing hormone and plasma progestins correlated with human ovulation, Fertil. Steril. 21:119, 1970.
- Thomas, K., Walckiers, R., and Ferin, J.: Biphasic pattern of LH midcycle discharge, J. Clin. Endocrinol. Metab. 30:269, 1970.
- Ferin, J., Thomas, K., and Johansson, E. D. B.: Ovulation detection, in Hafez, E. S. E., and Evans, T. N., editors: Human Reproduction, New York, 1973, Harper and Row.
- Croxatto, H. B., Carril, M., Cheviakoff, S., Patriti, N., Pedroza, E., Croxatto, H. D., Gomez-Rogers, C., and Rosner, M.: Time interval between LH peak and ovulation in women, in Biological and Clinical Aspects of Reproduction, Amsterdam, 1974, Excerpta Medica, p. 282.
- Pauerstein, C. J., Eddy, C. A., Croxatto, H. D., Hess, R., Siler-Khodr, T. M., and Croxatto, H. B.: Temporal relationships of estrogen, progesterone, and luteinizing hormone levels to ovulation in women and infrahuman primates, Am. J. Obstet. Gynecol. 130:876, 1978.
- Finney, D. J.: Probit analysis, ed. 3, Cambridge, 1971, Cambridge University Press.
- Ham, A. W.: in Histology, ed. 7, Philadelphia, 1974, J. B. Lippincott Company.
- 21. Schmidt-Gollwitzer, K., Schmidt-Gollwitzer, M., Sackmann, U., and Eiletz, J.: Ovulation timing by a radioreceptor assay for human luteinizing hormone, Int. J. Fertil. 22:232, 1977.

#### Malacoplakia of the female genital tract

- A. CHALVARDJIAN, B.A., M.D., F.R.C.P.(C.)
- L. PICARD, M.D.
- R. SHAW, M.D., F.R.C.P.(C.)
- R. DAVEY, M.D., F.R.C.S.(C.)
- I. D. CAIRNS, M.A., F.A.C.S., F.R.C.S.(C.)

Toronto, Ontario, Canada

Malacoplakia is an uncommon chronic granulomatous inflammation which most frequently involves the urinary bladder of middle-aged women and rarely affects the genital tract. In this paper 10 cases of female genital malacoplakia are reviewed, seven of which have been reported previously in the literature. Genital malacoplakia usually occurs in women 60 years of age or older and most frequently affects the vagina. Vaginal bleeding is a common presenting complaint and the lesion may simulate a malignancy. Four of the 10 patients were receiving corticosteroids at the time of diagnosis. *Escherichia coli* was cultured from urine or from the lesion itself in half of the cases. The disease appears to be an acquired defect in bactericidal function of histiocytes. Antibiotic therapy and surgical excision are effective, although a recurrence developed in one patient and was successfully re-excised. (AM. J. OBSTET. GYNECOL. 138:391, 1980.)

MALACOPLAKIA is an uncommon form of chronic granulomatous inflammation which usually affects the urinary tract and only rarely affects the female genital tract. The lesion is characterized histologically by the presence of histiocytes (von Hansemann cells), together with intracellular and extracellular calcified spherules (Michaelis-Gutmann bodies), in tissue.

To our knowledge, only seven cases of female genital malacoplakia have been reported to date in the literature. We wish to review the pertinent aspects of these cases and report three additional cases.

#### Case reports

Case 1. T. G., an 84-year-old, nulligravid woman, was hospitalized because of exacerbation of long-standing chronic obstructive pulmonary disease. The patient was 35 years postmenopausal and had recently had painless vaginal spotting. A transitional cell carcinoma of the urinary bladder had been locally resected

From the Departments of Pathology and Obstetrics and Gynecology, St. Michael's Hospital, North York General Hospital, and the University of Toronto.

Received for publication March 21, 1980.

Revised June 25, 1980.

Accepted June 27, 1980.

Reprint requests: Dr. A. Chalvardjian, Department of Pathology, 6C, St. Michael's Hospital, 30 Bond St., Toronto, Ontario, Canada M5B 1W8. and fulgurized 21 years previously. Because of hypertension and renal failure, which was thought to be due to vasculitis, the patient had been maintained on 10 mg of prednisone daily for the past three years.

Pelvic examination revealed atrophic external genitalia and a restrictive introitus. A stenotic lesion was felt about the midportion of the vagina. The cervix could not be visualized. The anterior wall of the vagina was covered by papillary, friable and necrotic-looking material, thought to be a neoplasm. On rectal examination a small atrophic cervix and uterus were palpated above and free of the lesion. There was no parametrial involvement. Cultures from the vagina grew Escherichia coli. The diagnosis of malacoplakia was made on biopsy and Papanicolaou smear. The patient was started on a regimen of Co-Trimoxazole and discharged. Four months later, partial cystectomy was done because of recurrent transitional cell carcinoma. There was no evidence of malacoplakia in the resected portion of bladder. The vagina at that time was totally stenotic.

Case 2. M. W., a 64-year-old, para 2, gravida 2 woman, who was 10 years postmenopausal, presented with a 1-week history of vaginal spotting. There was no history of urinary tract disease.

Examination with the use of anesthesia revealed a soft, friable cervix with yellowish nodular excrescences which extended bilaterally along the vaginal wall. Biopsy showed malacoplakia at both sites. A urine culture grew *Escherichia coli* and cystoscopy showed mild cystitis of the bladder base. Barium enema, upper gastrointestinal series, and excretory urography failed to

392 Chalvardjian et al.

October 15, 1980

Am. J. Obstet. Gynecol.

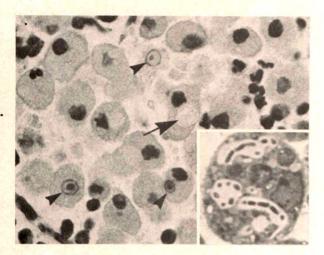


Fig. 1. Biopsy of the vagina (Case 1). The inflammatory infiltrate consists in this field mainly of von Hansemann histiocytes. Three characteristic intracellular Michaelis-Gutmann bodies are indicated by arrowheads. A cytoplasmic vacuole (arrow) contains faintly stained bacilli. ( $\times$ 700.) The bacilli are better demonstrated in plastic-embedded sections 1  $\mu$  thick and stained with toluidine blue, as shown in the *inset* in the right lower corner. ( $\times$ 1,760.)

show any extragenital involvement. Subsequently, total hysterectomy, bilateral oophorectomy, and electrocauterization of the vaginal lesions were performed.

Extensive malacoplakia of the cervix was present in the surgical specimen. Two years later a small recurrence was noted in the vaginal vault and treated by excision and electrocautery.

Case 3. M. B., a 61-year-old woman, 15 years postmenopausal, developed heavy vaginal bleeding following 2 months of cyclic estrogen therapy. This was associated with left lower quadrant pain and pyrexia which cleared spontaneously. Twenty-one years earlier, a right oophorectomy had been performed for endometriosis. Pelvic examination revealed a painless left adnexal mass. At operation, a friable and hemorrhagic ill-defined mass involved the left ovary and tube and extended from the left uterine cornu to the rectosigmoid region. The patient underwent total hysterectomy and left salpingo-oophorectomy. The diagnosis of malacoplakia was made on histologic examination of the left pelvic mass. A postoperative urine culture grew no organisms.

#### Pathologic findings

Tissues were processed and stained in routine fashion. By light microscopy, the histologic changes in the three cases were essentially similar and will be described together. The involved tissues were infiltrated diffusely by a mixed inflammatory infiltrate in which von Hansemann histiocytes and Michaelis-Gutmann bodies were easily recognized. The von Hansemann histiocyte, as illustrated in Fig. 1, is polygonal with

sharply defined cellular borders. The cytoplasm is finely granular or reticulated. In the biopsy from Case 1, gram-negative bacilli were observed within vacuoles in occasional histiocytes. The Michaelis-Gutmann body, the other hallmark of malacoplakia, is round, about the size of a nucleus, and is mostly intracellular. It is basophilic and may have a bull's-eye appearance (Fig. 1). The Michaelis-Gutmann body characteristically contains abundant calcium and variable amounts of iron.

By electron microscopy (Fig. 2), the plasma membrane of the von Hansemann histiocyte is smooth with few filopodia. The cytoplasm contains numerous membrane-bound, complex and variegated bodies representing secondary lysosomes or phagolysosomes. Bacilli, singly or in groups, are present within vacuoles in some of the cells. Ingested neutrophils in different stages of degeneration are observed within some histiocytes and, together with the digested bacteria, may contribute to the formation of the large phagolysosomes. The Michaelis-Gutmann body usually lacks a delimiting membrane (Fig. 2). It may be homogeneously electron-dense or may consist of a peripheral homogenous ring around a variegated central core, the latter resembling in structure some of the adjacent lysosomal bodies.

#### Clinical aspects

Analysis of the 10 cases, seven culled from the literature and three from our files, revealed that over two thirds of the patients were in the seventh decade or older. The ages ranged between 29 and 84 years, with a mean of 60 years. The most common site of involvement was the vagina, being affected in half of the patients (Cases 1 and 2),<sup>2, 6, 7</sup> while the endometrium was involved in two.1. 5 The most frequent symptom was vaginal bleeding, which occurred in six of the 10 patients (Cases 1 and 2).1, 2, 5, 6 Other symptoms included infertility with tubal involvement,3 an inguinal ulcer,7 and a mass lesion (Case No. 3) when the disease affected the parametrial or pelvic tissues. Vulvar involvement presented as an indurated ulcer.4 Four of the patients were on a regimen of maintenance therapy with corticosteroids at the time of diagnosis (Case 1).4, 5, 7 In six cases, bacilli were either demonstrated in tissue sections (Case 1)1, 2 and/or cultured from the lesion (Case 1)2, 4 or urine (Case 2).5 In all five cases in which cultures were obtained, Escherichia coli was the organism to be isolated. Treatment consisted of either surgical excision or antibiotic therapy. One of the three patients who were treated with antibiotics was lost to follow-up. The lesion healed in the second patient,2 while it resolved with vaginal stenosis in the third (Case 1). Cure was achieved in all four patients treated •

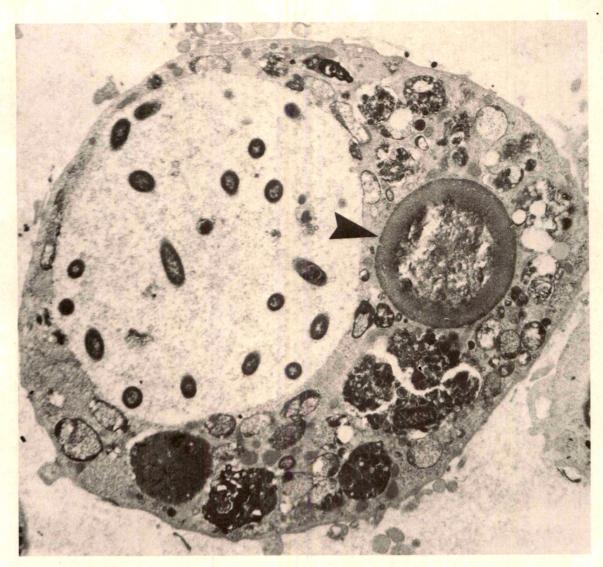


Fig. 2. Electron micrograph (Case 1) of a von Hansemann histiocyte showing to the right of center the characteristic Michaelis-Gutmann body (arrowhead) consisting of an amorphous peripheral ring surrounding a variegated central core. The cytoplasm contains numerous pleomorphic phagolysosomes of variable electron density. A large vacuole to the left contains bacilli appearing at different angles of section. ( $\times 8,000$ .)

surgically (Case 2),4-6 although in one instance the lesion recurred but was successfully re-excised (Case 2).

#### Comment

Malacoplakia has been recognized as an unusual inflammatory process which most frequently affects middle-aged women. It may involve sites other than the urinary tract. Coliform bacteria, particularly Escherichia coli, have been the organisms most commonly associated with the condition.

Our review of the 10 cases shows that female genital malacoplakia mainly occurs above the age of 60 years. The presenting symptom is often vaginal bleeding. Malignancy is suspected clinically because of the symptomatology and the appearance of the lesion, when a visible site is involved. The possibility of a neoplasm may even be entertained by the pathologist since the infiltrate may be quite cellular, consisting of a monomorphous population of clear histiocytes, which may simulate clear cell carcinoma or sarcoma. Histologically, malacoplakia is differentiated from xanthogranulomatous inflammation by the presence of Michaelis-Gutmann bodies.

The paucity of cases of female genital malacoplakia reported in the literature may be due, at least in part, to a failure of recognition of the lesion. Inflammatory processes, particularly those with a major histiocytic component, should be stained for calcium in an attempt to demonstrate the characteristic Michaelis-Gutmann bodies.

Malacoplakia appears to result from an acquired inability of phagocytes to destroy ingested bacteria. There is some evidence that suggests that the defect might involve all monocytes and histiocytes; if so, malacoplakia could be classified as a systemic disease.8 However, the lesion usually remains localized. This indicates that local factors may play an important role in the pathogenesis of the condition.

The present series of 10 cases may be too small to evaluate the best form of treatment of female genital malacoplakia. In patients who are immunosuppressed, discontinuation of chemotherapy, if possible, may help the lesion to regress. Once the causative organism has been identified and its sensitivity established, a bactericidal antibiotic would be the drug of choice. One capable of penetrating cellular membranes and attaining adequate intracellular concentrations should be chosen. Surgical excision of localized malacoplakia appears equally effective although the lesion may recur. Neither the urinary bladder nor the colon was affected in the 10 reviewed cases; however, it is recommended that involvement of these sites be excluded in all cases of female genital malacoplakia.

We wish to thank Miss Marie Pallo for assisting in the preparation of the manuscript and Miss S. Cohen and Mrs. I. Ilse for technical assistance.

#### REFERENCES

- 1. Rao, N. R.: Malacoplakia of broad ligament, inguinal re-
- gion and endometrium, Arch. Pathol. 88:85, 1969.

  2. Van der Walt, J. J., Marcus, P. B., De Wet, J. J., and Burger, A. J. J.: Malakoplakia of the vagina. First case report, S. Afr. Med. J. 47:1342, 1973.
- 3. Scheiner, C., Dor, A. M., Basbous, D., and Lebreuil, G.: La malacoplasie: formes anatomo-cliniques. Revue de la littérature, à propos de 15 observations personelles, Arch. Anat. Pathol. (Paris) 23:199, 1975
- 4. Arul, K. J., and Emmerson, R. W.: Malacoplakia of the skin, Clin. Exp. Dermatol. 2:131, 1977.
- 5. Thomas, W., Jr., Sadeghieh, B., Fresco, R., Rubenstone, A. I., Stepto, R. C., and Carasso, B.: Malacoplakia of the

- endometrium, a probable cause of postmenopausal bleeding. Am. J. Clin. Pathol. 69:637, 1978
- 6. Cremer, H., and Busanny-Caspari, W.: Die malacoplakie der scheide, eine seltene ursache einer vaginalen blutung, Geburtshilfe Frauenheilkd. 39:214, 1979.
- 7. Lin, J. I., Caracta, P. F., Chang, H. C., Uchwat, F., and Tseng, C. H.: Malacoplakia of the vagina, South. Med. J. 72:326, 1979.
- 8. Abdou, N. I., NaPombejara, C., Sagawa, A., Ragland, C., Stechschulte, D. J., Nilsson, V., Gourley, W., Watanabe, I., Lindsey, N. J., and Allen, M. S.: Malakoclakia: evidence for monocyte lysosomal abnormality correctable by cholinergic agonist in vitro and in vivo, N. Engl. J. Med. 297:1413,

#### Para-aortic lymphocyst

B. FREDERICK HELMKAMP, M.D. HANS-B. KREBS, M.D. MICHAEL B. ISIKOFF, M.D. STEVEN R. POLIAKOFF, M.D. HERVY E. AVERETTE, M.D. Miami, Florida

Although numerous articles regarding the etiology, incidence, complications, and management of pelvic lymphocysts have been published in the American literature since 1958, there has been no mention of para-aortic lymphocyst as a complication of para-aortic node dissection. Two recent cases of symptomatic para-aortic lymphocyst have prompted a review of our para-aortic node dissection technique when this procedure is not combined with a more extensive pelvic lymphadenectomy. Our modification in technique is to use retroperitoneal para-aortic drainage by constant pressure-controlled suction following closure of the posterior parietal peritoneum, and the results in our first 15 patients are presented. There were no complications related to the drainage technique. Abdominal ultrasound and intravenous urography have proved to be excellent diagnostic tools in the initial evaluation and subsequent follow-up of para-aortic lymphocysts. (Am. J. Obstet. Gynecol. 138:395, 1980.)

In 1958 Gray and associates<sup>1</sup> reported nine cases of pelvic lymphocyst following pelvic node dissections, all developing within 1 to 6 months postoperatively and five requiring surgical intervention. Subsequent articles<sup>2–7</sup> have appeared regarding the etiology, incidence, complications, and management of pelvic lymphocysts.

Since 1972, para-aortic node sampling and lymphadenectomy have assumed a major role in the evaluation and surgical staging of pelvic malignancies. Buchsbaum, Averette and associates, Nelson and associates, and Piver and Barlow all reported on series of para-aortic node dissections with no mention of lymphocyst as a complication. In addition, a recent publication from our institution on 450 para-aortic lymphadenectomies in gynecologic cancer described three cases of retroperitoneal hematoma but did not mention para-aortic lymphocyst as a postoperative complication.

From the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Miami School of Medicine.

Received for publication June 12, 1980. Accepted July 7, 1980.

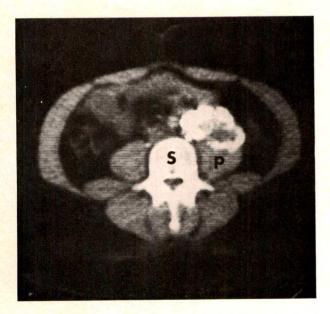
Reprint requests: B. Frederick Helmkamp, M.D., Department of Obstetrics and Gynecology, University of Rochester School of Medicine, P. O. Box 668, 601 Elmwood Ave., Rochester, New York 14642. Two recent cases of symptomatic para-aortic lymphocyst have prompted a review of our para-aortic node dissection technique when this procedure is not combined with a more extensive pelvic lymphadenectomy. These cases are presented, along with our current modification in surgical technique.

#### Case presentations

Case No. 1. P. S., an 18-year-old, black, nulligravid woman, was admitted to Jackson Memorial Hospital on April 10, 1977, with a large pelvic-abdominal mass and complaining of right lower quadrant and thigh pain. Menstrual periods were regular. Examination demonstrated a large 20 cm pelvic-abdominal mass consistent with a right ovarian neoplasm. Barium enema, intravenous pyelography (IVP), and serum levels of carcinoembryonic antigen, alpha fetoprotein, and the beta subunit of human chorionic gonadotropin were all normal. On April 13, 1977, the patient underwent exploratory laparotomy, right salpingo-oophorectomy, wedge resection of the left ovary, and para-aortic node dissection. Peritoneal washings were negative, and final diagnosis was dysgerminoma of the right ovary with three of 15 left para-aortic nodes positive for metastatic disease. Whole-chest tomography was negative but lymphography, performed on April 26, 1977, demonstrated multiple filling defects in the pelvic nodes consistent with metastatic disease. The patient was discharged on April 29, 1977, and then received 3,600 rads of whole-pelvis and para-aortic irradiation from



**Fig. 1.** Plain radiograph of the abdomen. Multiple droplets of contrast material from the previous lymphogram are identified within a large lymphocele.



**Fig. 2.** Computed tomography scan at the same level reveals contrast material within a fluid-containing mass just anterior to the left psoas muscle (*P*) and spine (*S*).

May 2 to June 6, 1977, followed by 3,600 rads to the mediastinum and supraclavicular areas from July 6 to July 29, 1977. The irradiation was tolerated well except for minimal esophagitis.

The patient did well until September, 1977, when she complained of persistent left upper quadrant pain. Abdominal roentgenography (Fig. 1) demonstrated a large collection of contrast material in the left midabdomen from the previous lymphogram. Computed tomography scan of the abdomen (Fig. 2) revealed a low density mass to the left of the L3-L4 vertebrae representing a large lymphocyst. Contrast was again noted within the mass. IVP showed left ureteral obstruction secondary to the lymphocyst.

Exploratory laparotomy on October 4, 1977, confirmed a large 12 by 6 cm lymphocyst below the pole of the left kidney, attached medially to the left common iliac artery, and with the obstructed ureter displaced anterior to the lymphocyst. The left retroperitoneal space was entered lateral to the descending colon, and the lymphocyst was exposed. The ureter was dissected from the mass, and the cyst was excised to its medial borders where marked adhesions from previous surgery and irradiation therapy were encountered. After the retroperitoneal drains were placed, left salpingo-oophorectomy was performed. There were no postoperative complications. Chest x-ray film and IVP on February 27, 1980, were completely normal and the patient has remained clinically free of disease.

Case No. 2. B. A., a 63-year-old white woman, para 3-2-1-3, was admitted to JMH on January 3, 1979, with a diagnosis of Stage IA, grade 2 adenocarcinoma of the endometrium. Metastatic workup including IVP, barium enema examination, cystoscopy, and proctoscopy was normal, and on January 11, 1979, she underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, para-aortic node dissection, and appendectomy. Final diagnosis was an adenosquamous carcinoma with more than 50% myometrial penetration and negative para-aortic nodes. Whole-pelvis irradiation was planned. The patient complained of persistent upper quadrant abdominal pain postoperatively, but gastrointestinal workup prior to discharge on January 23, 1979, was negative.

She was seen in consultation for irradiation therapy in February, 1979, when a right upper quadrant mass was palpable. Ultrasonography of the abdomen revealed a complex 10 by 8 cm fluid-filled mass displacing the right kidney anteriorly and laterally (Fig. 3) and representing either a retroperitoneal hematoma or a para-aortic lymphocyst. IVP confirmed the renal displacement, while fine needle aspiration of clear fluid with negative cytologic examination and no granulocytes confirmed the diagnosis of lymphocyst. Because there was no obstructive uropathy the patient was treated conservatively. She received 4,500 rads of whole-pelvis irradiation, and follow-up ultrasound

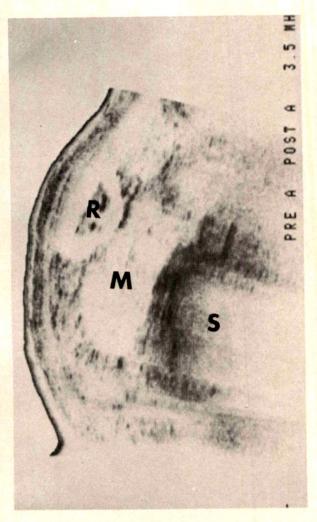


Fig. 3. Left lateral decubitus sonogram through the right midabdomen. The right kidney (R) is displaced laterally from the spine (S) by a fluid-filled mass (M).

examination in July, 1979, demonstrated only a 2 cm asymptomatic cyst.

#### Material and methods

All patients were admitted to the Gynecologic Oncology Service at Jackson Memorial Hospital, University of Miami School of Medicine. Para-aortic lymphadenectomy was performed to evaluate extrapelvic nodal disease, and this technique has been outlined previously in detail.12

Following completion of the lymphadenectomy, a 10 mm wide, perforated, flat, suction Jackson-Pratt\* drain is placed over both the inferior vena cava and the distal aorta (Fig. 4). By means of a long Sarot or Rumel forceps the drain is brought out in the right midquadrant





Fig. 4. Jackson-Pratt drain overlying inferior vena cava and distal aorta.

and sewn to the skin with a 2-0 silk suture. Care must be taken during the retroperitoneal tunneling so that injury to the ovarian vessels or ureter is avoided.

The posterior parietal peritoneum is then closed with a continuous, running 2-0 chromic suture. Upon completion of the laparotomy, the drain is attached to a Pleur-evac collection chamber with the use of constant pressure-controlled suction with a negative pressure of 8 to 10 cm of water. The drain is removed when there has been minimal drainage (5 to 10 ml) over 24 hours.

Ultrasonography of the abdomen with a commercially available gray-scale unit was performed 2 to 3 months following para-aortic lymphadenectomy in all cases to look for occult lymphocyst formation.

#### Results

Data on our first 15 patients are available. Thirteen patients had squamous carcinoma of the cervix, and two had endometrial adenocarcinoma. Three patients (all with cervical cancer) had metastatic disease in the para-aortic nodes. The average amount of lymph drainage collected was 203 ml (5 to 1,125 ml) and the mean duration of the drain to suction was 4.5 days (2 to

11 days). There were no complications related to the use of retroperitoneal drainage in this series, and follow-up sonography in all patients did not demonstrate the presence of occult lymphocysts.

#### Comment

Lymphocysts (or lymphoceles) represent lymphfilled retroperitoneal spaces in the region of the great vessels of the pelvis or abdomen. Their etiology has been attributed to improper ligation of pedicles following lymphadenectomy and/or lack of drainage of the retroperitoneal spaces. Contributing factors often mentioned are the presence of malignant lymph nodes and previous irradiation therapy, which enhances the effects of surgical injury and may decrease collateral circulation.7 Among the complications of lymphocysts mentioned by Jonsson and associates 13 are the following: displacement of intra-abdominal and extra-abdominal organs, pain, ureteral obstruction, secondary venous edema, and infection. Most authors1, 2, 14 conclude that surgical intervention is warranted only when lymphocysts become extremely symptomatic or when there is compromise of the genitourinary or gastrointestinal system.

The introduction of retroperitoneal drainage following pelvic lymphadenectomy<sup>5</sup> has greatly reduced the

incidence of lymphocyst, infection, and urinary fistulas. On the other hand, Rutledge and associates<sup>2</sup> and Dodd and colleagues<sup>7</sup> argue against the routine use of drains by stating that constant decompression of the retroperitoneal spaces encourages continuous lymph flow.

The results from our first 15 patients are encouraging in regard to the amount of drainage collected and the lack of complications encountered. The series is too small to allow any conclusions as to whether positive nodes, histology, or type of malignancy (cervix, corpus, ovary) affects the total drainage following lymphadenectomy.

Although intravenous urography frequently will demonstrate para-aortic lymphocysts, the optimal diagnostic tool currently available is ultrasound and/or computed tomography. The value of sonography in the identification of intra-abdominal fluid collections in general and lymphocysts in particular has been well documented in the literature. <sup>15, 16</sup> When there is a large amount of bowel gas in the middle and lower abdomen, the limitations of sonography become more apparent and computed tomography becomes the procedure of choice. Finally, as shown in our two case presentations, ultrasound and computed tomography have proved their value in the subsequent follow-up of para-aortic lymphocyst.

#### REFERENCES

- Gray, M. J., Plentl, A. A., and Taylor, H. C., Jr.: The lymphocyst: A complication of pelvic lymph node dissection, Am. J. Obstet. Gynecol. 75:1059, 1958.
- Rutledge, F., Dodd, G. D., Jr., and Kasilag, F. B., Jr.: Lymphocysts: A complication of radical pelvic surgery, Am. J. Obstet. Gynecol. 77:1165, 1959.
- 3. Nelson, J. H., Jr., and Huston, J. W.: Lymphocyst formation following pelvic lymphadenectomy, Am. J. Obstet. Gynecol. 78:1298, 1959.
- Ferguson, J. H., and MacLure, J. G.: Lymphocele following lymphadenectomy, Am. J. Obstet. Gynecol. 82:783, 1961.
- Symmonds, R. E., and Pratt, J. H.: Prevention of fistulas and lymphocysts in radical hysterectomy, Obstet. Gynecol. 17:57, 1961.
- Symmonds, R. E.: Morbidity and complications of radical hysterectomy with pelvic lymph node dissection, Am. J. OBSTET. GYNECOL. 94:663, 1966.
- 7. Dodd, G. D., Rutledge, F., and Wallace, S.: Postoperative pelvic lymphocysts, Am. J. Roentgenol. Radium Ther. Nucl. Med. 108:312, 1970.
- Buchsbaum, H. J.: Para-aortic lymph node involvement in cervical carcinoma, Am. J. Obstet. Gynecol. 113:942, 1972.
- 9. Averette, H. E., Dudan, R. C., and Ford, J. H.: Explora-

- tory celiotomy for surgical staging of cervical cancer, Am. J. Obstet. Gynecol. 113:1090, 1972.
- Nelson, J. H., Jr., Macasaet, M. A., Lu, T., Bohorquez, J. F., Smart, G. E., Nicastri, A. D., and Walton, L. A.: The incidence and significance of para-aortic lymph node metastases in late invasive carcinoma of the cervix, Am. J. Obstet. Gynecol. 118:749, 1974.
- Piver, M. S., and Barlow, J. J.: Paraaortic lymphadenectomy in staging patients with advanced local cervical cancer, Obstet. Gynecol. 43:544, 1974.
- Belinson, J. L., Goldberg, M. I., and Averette, H. E.: Paraaortic lymphadenectomy in gynecologic cancer, Gynecol. Oncol. 7:188, 1979.
- Jonsson, J., Wallace, S., Jing, B. S., Johnson, D. E., and Dodd, G. D.: Changes in the lymphatic dynamics after retroperitoneal lymph node dissection, J. Urol. 118:814, 1977.
- Johnson, D. E.: Retroperitoneal lymphadenectomy: indications, complications, and expectations, Recent Results Cancer Res. 60:221, 1977.
- Doust, B. D., and Thompson, R.: Ultrasonography of fluid collections, Gastrointest. Radiol. 3:273, 1978.
- Hill, M., and Sanders, R. C.: Gray scale B scan characteristics of intra-abdominal cystic masses, J. Clin. Ultrasound 6:217, 1978.

#### Primagravida

Increased intra-abdominal pressure and expanded blood volume, coupled with decreased physical activity during pregnancy, predispose to varices of the lower extremities. Distention of vein walls can cause secondary valve incompetence.

#### Multipara

Varicose veins become more severe in subsequent pregnancies and may reach the critical stage. Temporary valve incompetence, associated with each pregnancy, may lead to permanent lifetime vascular impairment in varicosities of the lower extremities.

#### Venous Pressure Gradient' Support

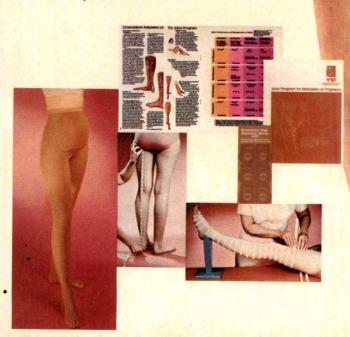
Jobst has custom-engineered thousands of Venous Pressure Gradient Supports for pregnancy. Why custom-make each pantyhose-type support according to measurements taken of each individual limb? A few millimeters of counterpressure, too much or too little, can harm already distended valves. A VIP™ pregnancy support applies known counterpressure, opposing hydrostatic venous pressure like an external fascial prosthesis. Fatigue and discomfort are relieved, and edema is reduced.

#### Clinical Proof

A VIP support, worn during the critical months of gestation, may prevent permanent damage to distended veins. Thompson reports, We have preferred the Jobst stocking in our clinic. An elastic leotard produced by this company is particularly useful for varicose veins during pregnancy. Most patients are pleasantly surprised by the comforting support this garment gives."

#### Reprints and Monograph

Do you want to receive a collection of clinical reprints on varicosities and a full-color, eight-page monograph and bibliography describing the physiological fluid dynamics of external elastic compression in pregnancy? Fill in the handy coupon or write on your letterhead.



Jobst, please send me clinical reprints and monograph on varices of pregnancy.

Varices of Pregnancy

Name\_\_\_\_\_\_Title\_\_\_\_

Address\_\_\_\_\_
City\_\_\_\_
State\_\_\_\_\_Zip\_\_\_\_

JOBST BOX 653 · TOLEDO · OHIO 43694 · USA JOBST IRELAND, LTD · THURLES CO. • TIPPERARY · IRELAND

1. Fegan G: Varicose Veins-Compression Sclerotherapy. London, Wm

#### MATERNAL/FETAL MEDICINE

Full time faculty position available. Rank of Assistant or Associate Professor. Busy tertiary referral center offers excellent opportunity for research and teaching within medical school environment. Excellent laboratory facilities available for basic and clinical support. Board eligibility or certification in subspecialty as well as special interest and experience in ultrasonography desirable. Anticipated starting date—position available after January 1, 1981. Recruiting deadline November 30, 1980.

Affirmative Action/Equal Opportunity Employer
Competitive Salary and Fringe Benefits
Reply with curriculum vitae to:

Charles S. Mahan, M.D.
Chairman, Search Committee
Department of Obstetrics and Gynecology
University of Florida College of Medicine
J. Hillis Miller Health Center
P.O. Box J-294
Gainesville, Florida 32610

#### IMMEDIATE OPENING

Small, prepaid group practice located in Salem, Oregon, is seeking one obstetrician-gynecologist for immediate opening. The group is currently comprised of four family practitioners who provide a full range of medical services, including obstetrics. Rapid expansion is anticipated, with the addition of a second obstetrician-gynecologist expected by 1983.

The clinic is a satellite of the Kaiser-Permanente Medical Care Program located in the Portland-Vancouver area, 40 miles north of Salem. The 27-member Department of Obstetrics and Gynecology in Portland will assist with call and vacation coverage for practitioners located in the Salem clinic. The medical practice is varied and professionally stimulating, offering the physician a pure practice free of business and administrative concerns. A comprehensive salary and benefits package, including a sabbatical program, malpractice coverage, three weeks vacation and one week educational leave to start, life, medical/dental and disability insurance, and two excellent retirement programs, is provided. The physician is eligible for ownership participation after two years with the program.

Salem, the capital of Oregon, has approximately 100,000 people and is located in a stable, prosperous economic region of the beautiful Northwest. Outdoor recreational facilities are superb, including excellent skiing, backpacking, fishing and boating.

Please sent two (2) copies of your curriculum vitae with your initial response to:

Marvin Q. Goldberg, M.D. President, Northwest Permanente, P.C. 1500 S.W. First Avenue, Eleventh Floor Portland, Oregon, 97201.

An Equal Opportunity Employer

## CHANGING YOUR ADDRESS?

When planning to move, please:

- 1. Notify us of the change six (6) weeks in advance so you won't miss a single issue.
- Tell us the name of this Journal. (We publish seventeen periodicals.)
- 3. Give us your old address and your new address—complete—including the zip code.
- 4. Be sure to include your mailing label whenever you write us concerning your subscription. It helps us serve you faster!

#### MAIL TO:

#### THE C. V. MOSBY COMPANY

Circulation Department 11830 Westline Industrial Drive Saint Louis, Missouri 63141 USA



North 1450 (norethindrone 1 mg with mestranol 0.05 mg)



Syntex (F.P.), Inc. Humacao, P.R. 00661

Please see summary of Prescribing Information on following page.

Norinyl® 1+50 21-Day Tablets rethindrone 1 mg. with mestranol 0.05 m Norinyl® 1+50 28-Day Tablets (21 norethindrone 1 mg, with mestranol 0.05 mg, tablets followed by 7 inert tablets

#### ORAL CONTRACEPTIVE (O.C.) AGENTS

NOISAL CONTINUET IVE (U.C.) AUDITION
NOISATIONS O.C.S are indicated for the prevention of pregnancy. DOSERELATED RISK OF THROMBOEMBOLISM FROM O.C.S. Studies have shown a
positive association between the dose of estrogens in O.C.s and the risk of
thromboembolism. For this reason, it is prudent and in keeping with good
principles of therapeutics to minimize exposure to estrogen. The O.C. product prescribed for any given patient should be that product which contains the
least amount of estrogen that is compatible with an acceptable pregnancy rate
and patient acceptance. It is recommended that new acceptors of O.C.s
should be started on preparations containing 0.05 mg or less of estrogen. should be started on preparations containing 0.05 mg or less of estrog CONTRAINDICATIONS 1. Known or suspected pregnancy (see Warning 15). 2. Thrombophlebitis or thromboembolic disorders. 3. A past history deep vein thrombophlebitis or thromboembolic disorders. 4. Undiagnos abnormal genital bleeding, 5. O.C.s should not be used by women who have have had any of the following conditions: a. Cerebral vascular or coronary lery disease. b. Known or suspected carcinoma of the breast. c. Known suspected estrogen dependent neoplasia. d. Benign or malignant liver turn which developed during the use of oral contraceptives or other estrogen cataling nordicats.

WARNINGS: Cigarette smoking increases the risk of serious cardiovascular side effects from 0.C. use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use 0.C.s should be strongly advised not to smoke.

The use of 0. C. s is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, liver tumor, gall bladder disease, visual disturbances, fetal abnormalities, and hypertension. Practitioners prescribing 0.C.s should be familiar with the following information relating to these risks.

tions including thromboembolism, stroke, myocardial mraction, and hypertension. Practitioners prescribing 0.C. should be familiar with the following information relating to these risks.

1. Thromboembolic Disorders and Other Vascular Problems: An increased risk of thromboembolic and thrombotic disease associated with the use of 0.C. s is well established. One British stury demonstead and thrombot experience of the problems of

TABLE 1. The annual number of deaths associated with control of fertility and no control per 100,000 nonsterile women by regimen of control and age of

	15-19	20-24	25-29	30-34	35-39	40-44	
No method	5.6	6.1	7.4	13.9	20.8	22.6	
Abortion only	1.2	1.6	1.8	1.7	1.9	1.2	
Pill only -nonsmokers	1.3	1.4	1.4	2.2	4.5	7.1	
Pill only -smokers	1.5	1.6	1.6	10.8	13.4	58.9	
Traditional	0.9	1.0	1.2	1.4	2.0	1.9	
contraception only Traditional contra-	1.1	1.6	2.0	3.6	5.0	4.2	
ception and abortion .	0.2	0.2	0.3	0.3	0.3	0.2	

The risk of thromboembolic and thrombotic disease associated with 0.C.s increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hyperlipidemias, obesity, diabetes, or histery of preeclampic toxemia and especially by clearette smoking. Raxed on

the data currently available, the following table gives a gross estimate of the risk of death from circulatory disorders associated with the use of 0.C.s:

TABLE 2. Smoking habits and other predisposing conditions—risk associated with use of 0.C.s.

B	A
C	
O	В
C,D	С
C.B	B.A
	C, B stated with mo stated with low

The physician and the patient should be airel to the earliest manifestations of thromboembolic and thrombotic disorders (e.g., thromboembolic, and thrombotic disorders (e.g., thromboembolic, and thrombotic disorders (e.g., thromboembolis, pulmary emboling, cerebrovascular insufficiency coronary occlusion, retinal suspected, the dimeschaer of thromboembolis or complete the disorders of the complete of the comple

pregnancy 6. Gail Bladder Disease: Studies report an increased risk of gal bladder disease in users of 0.C.s or estrogens. In one study, an increased risk appeared after? years of use and doubled after 4 of 5 years of use. It risk appeared after 2 years of use and doubled after 4 of 5 years of use. It risk appeared to the provide the provided of th neither confirmed nor refuted: premenstrual-like syndrome, calaracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of hair, erythema multiforme, erythema nodosum, hemorrhagic eruntion vaginitis porohyria impaired renal function

## SO EFFECTIVE YOU'D EXPECT TO WRITE A PRESCRIPTION

# SO SAFE YOU'T HAVE TO



Preparation H and its principal ingredient—Skin Respiratory Factor (SRF) have been studied in vitro.\* A group of world renowned wound-healing specialists confirmed that SRF stimulated wound oxygen consumption, epithelialization and collagen synthesis.

The unique Preparation H formula temporarily relieves pain and itching in many cases and actually helps shrink swollen hemorrhoidal tissue due to inflammation. All without anesthetics or steroids.

PREPARATION H

PARATIONER

Helps shrink swelling of hemorrhoidal tissues...caused by inflammation and gives prompt, temporary relief in many cases from pain and itching in tissues.

NET WT. 2 OZ.

#### PREPARATION H®

Clinically tested.

Available in ointment and suppositories.

PREPARATION H ACTIVE INGREDIENTS: Live Yeast Cell Derivative, supplying 2,000 units Skin Respiratory Factor Per Ounce of Base; Shark Liver Oil 3.0%, supplying Vitamin A.

\*Goodson W, Hohn D, Hunt TK, et al: Augmentation of some aspects of wound healing by a "Skin Respiratory Factor." J Surg Res 21:125-129, 1976.

For literature and patient education material, send coupon to Medical Dept., Whitehall Laboratories, 685 Third Avenue, New York, New York 10017.

AJOG	10/15

Please send

Reprint of "Augmentation of Some Aspects of Wound Healing by a 'Skin Respiratory Factor'"

Patient Education Booklets on the common causes, prevention and treatment of hemorrhoids

PHYSICIAN NAME

(please print)

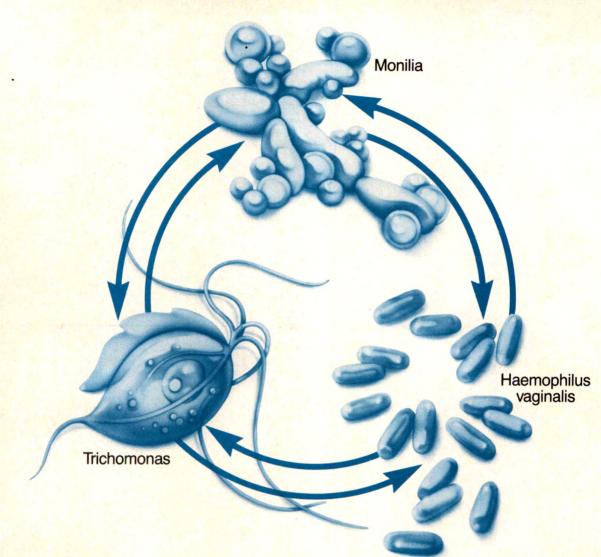
SPECIALTY

OFFICE ADDRESS

CITY

STATE

ZIF



# Fiple target therapy for infectious vaginitis BETADINE Microbicides Vaginitis Regimen

- Broad-spectrum microbicidal action kills all three pathogens usually responsible for infectious vaginitis—monilia, *Trichomonas* and *Haemophilus vaginalis*.
- Microbicidal action is maintained in the presence of blood, serum and vaginal secretions.
- Virtually nonirritating to skin and vaginal mucosa—nonstaining to skin and natural fabrics.

Easy-to-follow regimen
IN THE OFFICE
BETADINE® Solution

AT HOME BETADINE® Vaginal Gel\* (povidone-iodine)

#### **BETADINE®** Douche

- In the office, swab the cervix and vulvovaginal area with BETADINE Solution.
- Prescribe BETADINE Vaginal Gel (povidone-iodine), one applicatorful of which is to be inserted each night.
- Followed the next morning by BETADINE Douche in therapeutic concentration— 2 tablespoonfuls to a quart of lukewarm water.
- After two weeks
  - Patient returns for an office visit.
  - In more resistant cases, the regimen may be continued through 1 or 2 cycles, if necessary.

#### **BETADINE®** Vaginal Gel

(povidone-iodine)

**Brief Summary** 

For use in the treatment of Trichomonas vaginalis vaginitis, monilial vaginitis and nonspecific vaginitis.

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: possibly effective for use in the management of trichomonas vaginalis vaginitis, monilial vaginitis and nonspecific vaginitis. Final classification of the less-than-effective indications requires further investigation.

#### Precaution

It irritation, redness or swelling develops, discontinue use. The rare individual with history of iodine sensitization should not use this product, pending further investigation.

#### **Purdue Frederick**

© 1980, The Purdue Frederick Company/Norwalk, CT 06856 218680 A9716

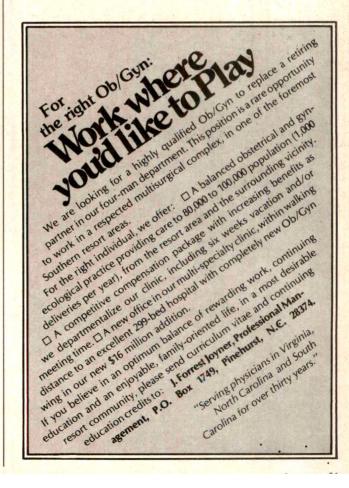
#### GYNECOLOGIC ONCOLOGIST

The Hitchcock Clinic is seeking fully qualified candidates for this full time position with the title of Director of Gynecologic Oncology. The eight member OB/GYN section provides primary to tertiary care at New Hampshire's only tertiary hospital and is affiliated with the Dartmouth-Hitchcock Medical Center which includes the Norris Cotton Cancer Center. The position includes an academic appointment at the Dartmouth Medical School.

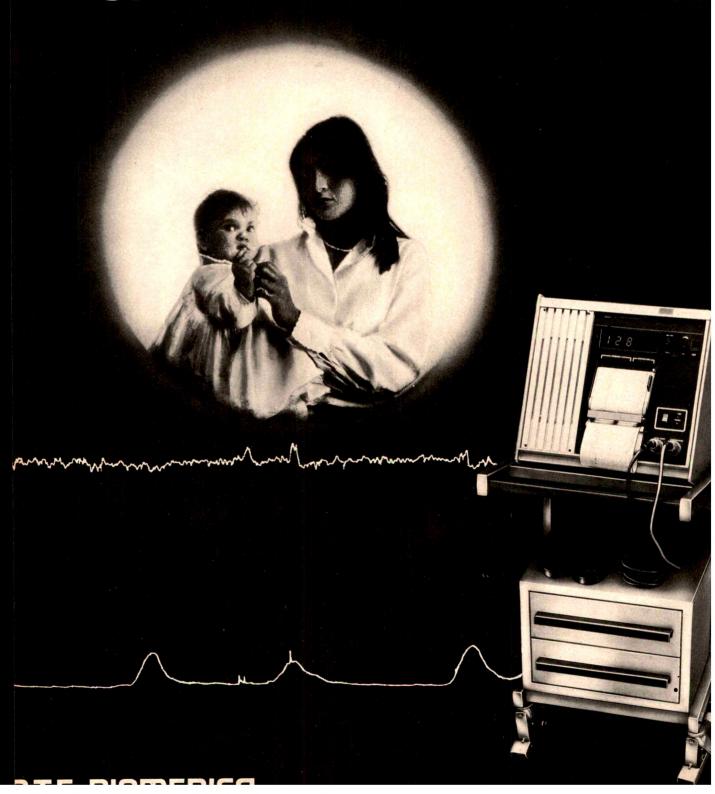
Current staff includes feto-maternal medicine and gynecologic-endocrinology subspecialists, 3 medical oncologists, and 3 radiation therapists.

Salary is dependent upon past training and experience with an excellent fringe benefit program through the primary employer, the Hitchcock Clinic.

For further details send curriculum vitae to: Barry D. Smith, M.D., Chairman Section of Obstetrics & Gynecology Hitchcock Clinic, Hanover, NH 03755. An Equal Opportunity Employer.







#### **OBSTETRICS**

## Blind oxytocin challenge test and perinatal outcome

K. J. STAISCH, M.D.

J. R. WESTLAKE, PH.D.

R. A. BASHORE, M.D.

Los Angeles, California

A total of 435 oxytocin challenge tests (OCT) were performed on 217 high-risk pregnant patients, and the test results were blinded. The results were correlated with late decelerations of the fetal heart rate during labor, Apgar scores at 5 minutes, a neonatal morbidity score, and perinatal mortality. The incidence of late decelerations during labor was 17% in the negative group, 24% in the suspicious group, and 33% in the positive group. The correlation of OCT results and the various measures of fetal outcome indicated that an individual fetus at risk cannot be identified with a high degree of accuracy since 67% of the tests were false positive and 17% were false negative. Even when the OCT was positive, 61% of infants did not have late decelerations in labor, low Apgar scores, or significant neonatal morbidity. When elective belivery has been decided upon after consideration of all clinical information, induction of labor rather than primary cesarean section is usually indicated. In this study 78% of patients were delivered vaginally with no significant increase of cesarean sections in the positive and suspicious groups as compared with the negative group. (Am. J. Obstet. Gynecol. 138:399, 1980.)

From the Department of Obstetrics and Gynecology, School of Medicine, and the Mental Retardation Center, University of California, Los Angeles.

Supported in part by United States Public Health Service Grant HD 05615. Computing assistance was obtained from the Health Sciences computing facility, University of California, Los Angeles, supported by National Institutes of Health Special Research Resources Grant RR-3.

Parts of this research were presented at the Twenty-sixth Annual Meeting of the Society for Gynecologic Investigation, San Diego, California, March 21-24, 1979.

Received for publication January 4, 1980.

Revised June 23, 1980.

Accepted June 30, 1980.

Reprint requests: Dr. Klaus J. Staisch, Detartment of Obstetrics and Gynecology, University of California, Los Angeles, School of Medicine, The Center for the Health Sciences, Los Angeles, California 90024.

THE RAPID CLINICAL EXPANSION of monitoring techniques to detect fetuses at risk prior to labor has resulted in reliance on unvalidated methods. The pattern of late decelerations of the fetal heart rate in response to the stress of uterine contractions is frequently, although not always, associated with fetal acidosis and asphyxia at birth. Based on this rationale the oxytocin challenge test (OCT) was formulated on the assumption that oxytocin-induced contractions might identify the hypoxic and compromised fetus before labor in high-risk pregnancies. As with many new procedures, the definition of test results and the criteria chosen to depict fetal outcome varied among reported studies.1-5 As a consequence, recommendations with the findings of a positive OCT with persistent late decelerations have ranged from delivery by cesarean section<sup>3-6</sup> to immediate induction of labor<sup>7-9</sup> or repeated

**Table I.** Indications for OCT

Indication	No. of cases	%
Hypertension	82	38.1
Postdates*	38	17.5
Diabetes mellitus	35	16.1
1UGR suspected†	17	7.8
Previous stillbirth	9	4.1
Age >35 or <18 years	9	4. I
Rh-sensitized	7	3.2
Heroin addiction	5	2.3
Placenta previa	4	1.8
Weight >200 pounds	4	1.8
Others	7	3.2
Total	217	100.0

<sup>\*</sup>Postdates = ≥42 weeks' gestation.

testing. 1. 10 It is difficult to make comparisons of studies where the OCT result was known to the attending physician, since knowledge of the test result has influenced management and, perhaps, outcome of pregnancy.3-5. 7 This study was undertaken to investigate the prognostic value of the OCT in the absence of managing physician bias with the results blinded. Fetal outcome was correlated with test results on the basis of fetal heart rate abnormalities during labor, the Apgar scores, performance of the newborn infant in the nursery, and perinatal mortality rate.

#### Material and methods

The 217 patients in the study group were seen in the prenatal clinic at the University of California, Los Angeles, during a 2-year period from 1975, and were considered to have high-risk pregnancies on the basis of the complications listed in Table I. Where more than one antenatal complication was present, only the problem considered primary was listed. The tests were begun when a complication was diagnosed and were usually started at 32 weeks and repeated weekly until delivery. The results of these tests were not known to the attending physician. The strategy of management was based on a thorough evaluation of the maternal and fetal condition, which included the use of serial estriol and ultrasound results as well as the lecithinsphingomyelin ratio. Monitoring by nonstress tests was not practiced on any patient prior to or during the study period. Pregnancy was terminated when, in the clinician's best judgment, a continuation would represent undue risk for the mother or fetus. All tests were performed by specially trained nurses in a separate, quiet room. After informed consent was obtained, which included a statement that the results would be blinded, the patient was placed in the left lateral or semi-Fowler's position. Recording was carried out with an external fetal monitor (Corometrics, Model 101) with an ultrasound transducer and a tocodynamometer at a paper speed of 3 cm/minute.

If spontaneous uterine contractions were not present or were less than 3 in 10 minutes, oxytocin was administered at increasing rates by a constant-infusion pump until three contractions in a 10-minute period were produced. The initial oxytocin infusion rate was 0.5 mU/minute and was increased at 20-minute intervals by doubling the dosage to a maximum of 32.0 mU/ minute.

For purposes of this study, the following definitions were used: A "negative test" showed no late decelerations of the fetal heart rate with uterine contractions. A "suspicious test" showed late decelerations with some, but not all, contractions. A "positive test" showed late decelerations with every contraction in a 10-minute period. Patients with unsatisfactory tracings that were due to technically poor heart rate tracings (8%) were excluded. Patients whose fetuses demonstrated late decelerations secondary to hyperstimulation (3%), i.e., frequency of contractions more than every 2 minutes, contractions longer than 90 seconds, and increased baseline tone to palpation between contractions, were also dismissed from analysis.

The patients were grouped for purposes of this study on the basis of their single most ominous OCT result regardless of the outcome of the last test prior to delivery. Patients with one or more positive OCTs prior to delivery were designated "positive"; one or more suspicious OCTs but none positive, "suspicious"; and patients with all negative OCTs, "negative."

The fetal heart rate during labor was recorded continuously with external and/or internal techniques. A few patients experienced rapid labors and, therefore, did not have electronic monitoring. The tracings were analyzed by one interpreter according to the criteria provided in the Technical Bulletin published by the American College of Obstetricians and Gynecologists.11 Tracings were designated "late decelerations in labor" when this pattern was repetitive. Decelerations produced by artifacts, i.e., epidural blocks, supine hypotension, and hyperstimulation caused by excessive oxytocin infusion, were not scored as late decelerations for statistical analysis. When abnormal fetal heart rate patterns were observed, a fetal blood sample was obtained from the presenting part. When the fetal acid-base balance was normal, labor was continued despite the presence of abnormal fetal heart rate patterns. Too few blood samples were obtained in close proximity to delivery to analyze for association of fetal outcome.

Apgar scores of 6 or less at 1 and 5 minutes were considered abnormal.

<sup>†</sup>IUGR = Intrauterine growth retardation.

The performance of the newborn infant in the nursery from admission to discharge was evaluated by means of a neonatal morbidity score based on risk factors suggested by Littman and Parmelee<sup>12</sup> (Table II). The absence of each event was given a value of 1, while the presence of any event was given a value of 0. Thus, the optimum neonatal course was represented by a score of 9 and a score of 4 or less was considered to represent serious neonatal morbidity. The cumulative neonatal morbidity is similar in concept to the Apgar score in that it purposely avoids isolating single occurrences.

Correlation between results of tests evaluating fetal well-being and fetal and neonatal performance was analyzed for significance by means of a standard chisquare test.

A decision to terminate a pregnancy by early delivery was made after consideration of all available clinical and laboratory information. When early delivery was thought advisable an attempt was made to induce labor. A total of 95% of patients in this series experienced spontaneous or induced labor prior to delivery.

#### Results

A total of 435 OCTs were performed on 217 patients. There were 35 patients (16%) in the positive group, 52 patients (24%) in the suspicious group, and 131 patients (60%) in the negative group. The mean number of tests was 2.3, with a range from 1 to 8. The average oxytocin infusion rate to produce a frequency of three contractions in 10 minutes was 5.0 mU/ minute. The mean gestational age at delivery was 38.7 weeks (range, 32 to 45 weeks) for the negative group, 38.5 (range, 31 to 43 weeks) for the suspicious group, and 37.9 (range, 28 to 42 weeks) for the positive group. The mean interval between the last positive OCT tracing and delivery was 8.5 days in the positive group. In the suspicious group, the mean interval between the last suspicious tracing and birth was 6.5 days, and in the negative group, the mean time lapse between the last tracing and delivery was 4.1 days. There were no significant differences among groups in gestational age at birth or in the interval between last OCT and date of delivery. Approximately 50% of patients in each of the three groups went into spontaneous labor, 45% had inductions by amniotomy and/or oxytocin infusion, and 5% had elective cesarean sections. The correlation between positive, suspicious, and negative OCTs and the various expressions of fetal and neonatal performance are shown in Table III. The results of each group are compared to incidence of late decelerations in labor, low Apgar scores at 5 minutes, and neonatal morbidity scores. In the positive group, 10 of 30 pa-

Table II. Neonatal morbidity score

#### Items:

- 1. Respiratory distress
- Infection
- 3. Ventilation assistance
- 4. Noninfectious illness
- 5. Metabolic disturbance
- Convulsion
- Treatment for icterus
- Temperature disturbance
- 9. Feeding within 48 hours

This listing of neonatal complications from birth until discharge from the newborn nursery was adapted from Littman and Parmelee.12 Items 1 to 8 are given a point of 1 when absent, a point of 0 when present. Item 9 is given a point of 1 if oral feeding occurs within 48 hours following birth and a point of 0 if feeding was not possible. A total score of 9 means no neonatal complication. A total score of 4, for instance, ndicates the presence of five complications in a given infant.

Table III. Fetal and neonatal performance associated with OCT result

	Late deceleration in labor		Apgar se ≤6 a 5 minu	t	Neonat morbid score ≤	ty
OCT result	No.	%	No.	%	No.	%
Positive $(N = 35) (16\%)$	10 (30*)	33	7 (33)	21	6 (31)	19
Negative $(N = 130) (60\%)$	21 (123)	17	8 (129)	6	9 (127)	7
Suspicious (N = 52) (24%)	12 (50)	24	2 (52)	4	1 (52)	2

\*Numbers in parentheses are the numbers of patients evaluated for that particular parameter.

tients had late decelerations in labor, an incidence of 33%. In the negative group, 21 of 123 patients, or 17%, and in the suspicious group, 12 of 50 patients, or 24%, had late decelerations. The numbers in parentheses in Table III do not match the total numbers in each group because patients with elective cesarean sections or stillbirths, for instance, were excluded when the percentage of late decelerations in labor was calculated. Of the 35 patients classified as "positive" on the basis of their worst tracing, the last OCT before delivery was negative in six patients and suspicious in five patients. Low Apgar scores at 5 minutes occurred in 21% of infants in the positive group, in 6% in the negative group, and in 4% in the suspicious group. Major neonatal morbidity at a score of 4 or less occurred in 19% of infants in the positive group, in 7% in the negative group, and in 2% in the suspicious group. Analysis of each single event of the nine items in the neonatal score was performed. No single event alone, such as respiratory distress or convulsions, showed a significant prevalence within the OCT groupings. The positive

**Table IV.** Cesarean section deliveries according to OCT results

		Prin cesar secti	ean	India by lat celera	
OCT result	No. of patients	No.	%	No.	%
Positive Negative Suspicious	34 123 50	10 25 11	29 20 22	8 5 6	80 20 55

group had a statistically significant higher incidence of late decelerations, low Apgar scores, and low neonatal scores. There was no significant difference in these measures between the negative and suspicious groups.

Primary cesarean section deliveries, according to OCT results, are listed in Table IV. In the positive group there were 10 cesarean sections in 36 patients, or 29%; in the negative group, 20%; and in the suspicious group, 22%. The rate of cesarean sections among the three groups did not differ significantly but cesarean sections, because of fetal distress signified by late decelerations, were substantially higher in the positive group (80%) and in the suspicious group (55%) than in the negative group (20%). In the positive and suspicious groups, late decelerations tended to occur predominantly in early labor before 5 cm of cervical dilatation, while in the negative group they were equally distributed during the first and second stages of labor. There were eight perinatal deaths in this series (four stillbirths and four neonatal deaths) for an overall perinatal mortality rate of 37/1,000. There were four deaths in the positive group for a perinatal mortality rate of 114/ 1,000. Of these, two infants died in utero and two died following delivery. One fetal death occurred at 32 weeks associated with severe pre-eclampsia and the second occurred at 36 weeks, in an infant born to a diabetic mother. The two neonatal deaths were related to prematurity at 32 and 34 weeks.

There were four deaths in the negative group, for a perinatal mortality rate of 31/1,000. One fetal death resulted from abruptio placentae and the second occurred following intrauterine transfusion for severe Rh disease. Two neonates died as a consequence of premature labor and sepsis at 30 and 32 weeks. There were no neonatal deaths in the suspicious group.

#### Comment

The OCT is one of several procedures directed toward monitoring the fetal status in problem pregnancies. The test has been interpreted to measure respiratory placental function and to provide an accurate assessment of individual fetal risk. Because of previously published reports, it has become common practice to consider a positive OCT with persistent late decelerations as an indicator of fetal distress and to terminate pregnancy by early delivery.

This study was performed because of a doubt that a single test can be used as a sole indicator of fetal condition. The complex relationship between maternal, placental, and fetal function would suggest that such expectations are unrealistic. In this blinded series of high-risk pregnancies, fetal and neonatal performance was correlated with OCT results by means of standardized criteria for testing and strictly defined measurements for outcome of pregnancies. Grouping of patients according to their single most ominous test, rather than according to the result of the last test before delivery, was chosen in order to follow the sequence of test results in a given pregnancy.

In this population, 16% of patients had positive OCTs and 24% had suspicious OCTs sometime in late pregnancy. This incidence is higher than the 8% to 17% reported by Freeman and colleagues<sup>1</sup> and Schifrin and associates<sup>2</sup> for positive OCTs and higher than the 9% to 22% for suspicious OCTs as reported by Hayden and associates<sup>5</sup> and Bhakthavathsalan and co-workers.<sup>7</sup> This difference may be due to a variation in pregnancy populations. As reported by others,1, 2, 7 the present series demonstrated a significant correlation between positive OCTs and the appearance of late decelerations of the fetal heart rate during labor as compared to negative OCTs and late decelerations. However, 67% of patients in the positive group were judged to have false positive tests because of the absence of late decelerations during labor. This false positive rate is higher than that reported by Freeman and associates (24%) and Weingold and colleagues9 (48%). One explanation for these differences relates to the fact that active intervention by termination of pregnancy did not necessarily follow a positive OCT. However, such patients were retained in the positive group even though subsequent OCTs may have been suspicious or negative. In addition, expectant management following a positive OCT permitted better control of conditions such as hypertension and diabetes. Subsequent improvement in maternal and fetal function may have resulted in a lower incidence of fetal distress during labor. The Apgar and neonatal morbidity scores of the positive group indicated that approximately 20% of infants are at high risk immediately following birth and also dur-. ing the neonatal period, while the negative group experienced a substantially lower incidence of low Apgar scores (6%) and also a low incidence of neonatal morbidity (7%). The two stillbirths in the positive group need further explanation. One fetus died at 32 weeks

gestation in a patient with severe pre-eclampsia and concomitant acute pyelonephritis. Fetal heart tones disappeared a few hours after admission to the hospital while efforts were primarily directed toward stabilization of the condition of this seriously ill patient. It is highly unlikely that intervention would have occurred on the basis of a positive OCT result. The second stillbirth occurred in a patient with Class C insulindependent diabetes who had been admitted to the hospital for control. The lecithin-sphingomyelin ratio was 1.6 at 36 weeks' gestation and fetal heart tones were lost 2 days later. Delivery was planned at 37 weeks when the lecithin/sphingomyelin ratio was expected to be mature. It is possible that in this patient earlier intervention may have occurred if the positive OCT result had been revealed.

In the negative group, 17% of patients had late decelerations in labor or a false negative OCT. This incidence is higher than that reported by Freeman and colleagues<sup>1</sup> and Schifrin and associates<sup>2</sup> who reported a rate of 3% to 9% in a population with a variety of prenatal complications. However, Arias and Zamora<sup>13</sup> reported a 19% false negative rate in patients with chronic hypertension.

Patients with suspicious OCTs showed a 24% rate of late decelerations in labor but no increase in low Apgar scores or neonatal morbidity when compared to the negative group.

The findings in the present study stress the limitation of the OCT and emphasize the importance of clinical judgment in the high-risk pregnancy. Even when the OCT was positive, 61% of infants did not show late decelerations, low Apgar scores, or significant neonatal

morbidity. If the limitations in the evaluation of fetal status are accepted, findings of the present study may be used in clinical management. In a high-risk pregnancy, if the fetus has immature lungs determined by surfactant measurement of amniotic fluid and the maternal condition is amenable to treatment, thereby indirectly improving the fetal environment, then pregnancy should be managed expectantly as premature delivery always carries an increased risk of morbidity and mortality in the nursery.

When delivery has been decided upon after consideration of all clinical information and other laboratory tests such as estriol values, induction of labor rather than primary cesarean section is usually indicated. In this study 78% of patients were delivered vaginally and there was no significant increase of cesarean sections in the positive and suspicious groups as compared with the negative group. Induction should be done in a setting where continuous fetal monitoring during labor can be performed in order to recognize fetal distress. Delivery of high-risk pregnancies should be performed in a hospital setting where intensive neonatal care is available, since this study has shown that a fetus is at high risk because of premature labor and neonatal complications occur at a much higher rate than that reported in the general population even if all prenatal testing procedures are normal.

We are indebted for nursing assistance to Mrs. Fran Dennis, Mrs. Carol Nelson, and Mrs. Debbie Timmons, and to members of the obstetric house staff of the University of California, Los Angeles Hospital for their cooperation.

#### REFERENCES

- Freeman, R. K., Goebelsmann, U., Nochimson, D., et al.: An evaluation of the significance of a positive oxytocin challenge test, Obstet. Gynecol. 47:8, 1975.
- Schifrin, B. S., Lapidus, M., Doctor, G. E., et al.: Contraction stress test for antepartum fetal evaluation, Obstet. Gynecol. 45:433, 1975.
- 3. Spurret, B.: Stressed cardiotocography in late pregnancy, Br. J. Obstet. Gynaecol. 78:894, 1971.
- Cooper, J. M., Soffronoff, E. C., and Bolognese, R. J.: Oxytocin challenge test in monitoring nigh-risk pregnancies. Obstet. Gynecol. 45:27, 1975.
- Hayden, B. L., Simpson, J. L., Ewing, D. E., et al.: Can the oxytocin challenge test serve as the primary method for managing high-risk pregnancies? Obstet. Gynecol. 46: 251, 1975.
- Farahani, G., Vasudeva, K., Petrie, R., et al.: Oxytocin challenge test in high risk pregnancy, Obstet. Gynecol. 47:159, 1976.

- 7. Bhakthavathsalan, A., Mann, L. I., Tejani, N. A., and Weiss, R. R.: Correlation of the oxytocin challenge test with perinatal outcome, Obstet. Gynecol. 48:552, 1976.
- Ewing, D. E., Farina, J. R., and Otterson, W. N.: Clinical application of the oxytocin challenge test, Obstet. Gynecol. 43:563, 1974.
- Weingold, A. B., De Jesus, T. P. S., and O'Keefe, J.: Oxytocin challenge test, Am. J. Obstet. Gynecol. 123:466, 1975.
- Christie, G. B., and Cudmore, D. W.: The oxytocin challenge test, Am. J. Obstet. Gynecol. 118:327, 1974.
- 11. ACOG Technical Bulletin, Number 32, June, 1975.
- 12. Littman, B., and Parmelee, A. H.: Medical correlates of infant development, Pediatrics 61:470, 1978.
- 13. Arias, F., and Zamora, J.: Antihypertensive treatment and pregnancy outcome in patients with mild chronic hypertension, Obstet. Gynecol. 53:489, 1979.

# Suppression of threatened premature labor by administration of cortisol and $17\alpha$ -hydroxyprogesterone caproate: A comparison with ritodrine

ANTTI KAUPPILA
ANNA-LIISA HARTIKAINEN-SORRI
OLLI JÄNNE
RISTO TUIMALA
PENTTI A. JÄRVINEN
Oulu, Finland

A shift in progesterone-to-estradiol balance to estradiol dominance is assumed to be a prerequisite for regular uterine contractions. To antagonize this effect in premature labor 24 consecutive women were treated with intravenous cortisol for 3 days and with weekly intramuscular injections of  $17\alpha$ -hydroxyprogesterone caproate (17 OHP-C). Twenty-four similar patients treated with ritodrine served as a reference group. The delivery was postponed by at least 1 week in 21 patients (87.5%) in the steroid treatment group and in 18 patients (75%) in the ritodrine group. The premature labor lasted for  $5.1 \pm 0.4$  hours (mean  $\pm$  SEM) with steroid therapy and for  $2.2 \pm 0.3$  hours with ritodrine. In singleton pregnancies the gestational length and birth weight of the newborn infants were greater in the steroid treatment group (N = 23, 39.1  $\pm$  0.3 weeks, 3,460  $\pm$  119 gm) than in the ritodrine group (N = 24, 37.7  $\pm$  0.4 weeks, 3,106  $\pm$  118 gm). Steroid treatment suppressed serum estradiol concentrations (maximally by 60%) and, to a lesser extent, testosterone, estriol, and progresterone levels (maximally by 30%). (AM. J. OBSTET. GYNECOL. 138:404, 1980.)

PROGESTERONE (P) and estradiol-17 $\beta$  (E<sub>2</sub>) regulate human myometrial function during pregnancy and at delivery. P is assumed to have a sedative effect and its withdrawal is believed to be a prerequisite for the spontaneous onset of labor.<sup>1</sup> On the other hand, E<sub>2</sub> stimulates uterine muscle fibers both in vitro and in vivo.<sup>2</sup> Serum E<sub>2</sub> levels increase prior to the initiation of term labor<sup>3</sup> and are higher in laboring than in nonlaboring women at term.<sup>4</sup> However, large doses of P,<sup>5</sup> synthetic progestins,<sup>6</sup> or glucocorticoids,<sup>7</sup> which reduce the placental synthesis of E<sub>2</sub>, are unable to inhibit threatened premature labor. A shift to P dominance in the P-to-E<sub>2</sub>

From the Departments of Obstetrics and Gynecology and Clinical Chemistry, University of Oulu. Received for publication September 12, 1979.

Revised June 5, 1980.

Accepted June 30, 1980.

Reprint requests: Dr. Antti Kauppila, Department of Obstetrics and Gynecology, University of Oulu, SF-90220 Oulu 22, Finland. balance by either increasing the serum level of P or decreasing the E2 level alone is thus ineffective in suppressing premature uterine contractions. It is not known whether a simultaneous change in both of these steroids in the direction of P dominance would be more effective than alteration of a single hormone level. In the present study the action of P was potentiated by  $17\alpha$ -hydroxyprogesterone caproate (17 OHP-C), which prevented premature labor better than a placebo in women at risk for this complication.8 E2 synthesis was simultaneously suppressed by cortisol, which rapidly reduces the fetoplacental synthesis of estrogens7 and accelerates the synthesis of fetal pulmonary surfactant.9 We shall describe here the clinical and endocrinologic results obtained by this therapy and compare the results with the effects of ritodrine, a beta-adrenergic agonist often used for this purpose.

#### Patients and methods

**Patients.** Forty-eight women admitted between weeks 27 and 36 of gestation because of threatened prema-

**Table I.** Clinical data (mean  $\pm$  SEM) of the patient population in both groups

Group	No.	Age (yr)	Parity	Gestational weeks at start of therapy	Tocolysis-index
Steroid therapy	24	$25.5 \pm 1.1$	$1.8 \pm 0.2$ $1.8 \pm 0.2$	$33.4 \pm 0.4$	$3.2 \pm 0.3$
Ritodrine therapy	24	$25.9 \pm 1.0$		$32.8 \pm 0.6$	$3.1 \pm 0.3$

ture labor entered this investigation. The first 24 patients were treated with the steroids and the subsequent 24, with ritodrine. The clinical data for these groups were similar (Table I). Periods of contractions had lasted for 30 minutes prior to initiation of medication, the tocolysis index (Table II)10 varying from 2 to 6. During these periods, regular, painful contractions were recorded at least every 10 minutes. No premature rupturing of the membranes, uterine bleeding, or manifest diabetes was observed. The steroid treatment group included 13 primiparous women and the ritodrine group, 12. One case of gestational diabetes and one twin pregnancy were diagnosed in the steroid treatment group, and one case each of gestational diabetes, pyelonephritis, pre-eclampsia, and bronchial asthma were diagnosed in the ritodrine group. The gestational length was calculated from the first day of the last menstruation. Following successful tocolytic therapy (the treatment was considered successful when delivery was postponed by at least 7 days), four patients in each group were delivered at term either vaginally, after artificial induction of labor, or by cesarean section.

Tocolytic therapy. Steroid treatment was initiated by a simultaneous intramuscular injection of 250 mg of 17 OHP-C and an intravenous bolus of 100 mg of cortisol followed immediately by infusion of 150 mg of cortisol in 500 ml of 5% glucose over 2 hours. The intravenous injection of 100 mg of cortisol was repeated on the second and third days at 8:00 AM. Also 250 mg of 17 OHP-C was administered intramuscularly at 8:00 AM on the third day and then weekly until the thirtyseventh week of gestation.

Ritodrine (50 mg in 500 ml of 5% glucose) was infused initially at a rate of 50  $\mu$ g/min for 10 minutes. The dose was increased by 50  $\mu$ g/min at 10-minute intervals until uterine relaxation occurred. If there were any serious subjective disorders or a decrease of as much as 20 mm Hg in systolic blood pressure or 10 mm Hg in diastolic blood pressure, the infusion was terminated until the pressure returned to normal and was then restarted. The infusion was maintained at the lowest effective dose for at least 48 hours. This intravenous therapy was then followed by intramuscular injections of ritodrine (20 mg three times a day) for 2 days. During the intravenous therapy the patients in

**Table II.** Tocolysis index = sum of the scores

	Score							
	0	1	2	3	4			
Contractions	θ	Irregular	Regular		_			
Rupture of membranes	θ		High or questionable	_	Low			
Bleeding	$\theta$	Spotting	Bleeding					
Dilatation of cervix (cm)		1 ,	2	3	4 or more			

both groups were in a lateral or oblique side position and external cardiotocography was performed

Assays. Twelve patients in the steroid group and 13 in the ritodrine group were monitored endocrinologically. The serum levels of P, E2, estriol (E3), and testosterone (T) were determined from the venous blood samples taken immediately before the initiation of therapy, 3 and 6 hours afterward, and at 4:00 pm on the next 4 days. Serum was obtained by clotting and centrifugation and samples were stored at  $-20^{\circ}$  C until assayed in duplicate.

P, E<sub>2</sub>, and T were determined by radioimmunoassays with iodinated ligands, as previously described.11 Total E<sub>3</sub> was measured with commercial radioimmunoassay kits (The Radiochemical Centre, Amersham, England). In brief, aliquots of the standards and unknown samples were first subjected to enzyme hydrolysis. Duplicate aliquots of the hydrolyzed samples were taken for radioimmunoassay and incubated with the antibody and tracer for 24 hours. Separation of antibody-bound and free hormone was achieved by ammonium sulfate precipitation. The intra-assay and interassay coefficients of variation were below 10% in all the assays.

The formula 
$$\frac{\text{observed value} - \text{initial value}}{\text{initial value}} \times 100$$

was used to standardize the findings of the different parameters.

Student's t test was used for the statistical analysis of the results.

#### Results

Clinical results. An inhibition of premature uterine contractions was initially obtained in 21 women in the steroid treatment group (three failures) and in 22 in

Table III. Patients delivered within 1 week of treatment

Patient No.	Age (yr)	Parity	Gestational week at therapy	Tocolysis index	Therapy	Gain in hours	Birth weight (gm)	Complications of pregnancy
1	25	2	36	6	Steroids	11	2,660	
2	22	1	35	4	Steroids	36	3,460	*****
3	20	1	28	. 6	Steroids	14	A: 920*	Twin pregnancy
			•				B: 900†	
4	37	2	35	6	Ritodrine	34	2,740	
5	25	1	36	3	Ritodrine	40	3,680	
6	26	5	35	6	Ritodrine	7	2,720	-
7	24	2	. 36	3	Ritodrine	30	2,580	,
8	19	1	35	3 <	Ritodrine	42	2,270	Pyelonephritis ac
9	23	2	32	3	Ritodrine	104	2,120	Partial placenta pre

<sup>\*</sup>Neonatal neurological disorders:

Table IV. Success rate of tocolysis (total material)

		Duration of			gation of acy (days)	No. of neo	nates in different weig	ht groups
Group	No.	premature labor (hr)	≤3	· <b>≤</b> 7	>7	<2500 gm	2,500-2,999 gm	≥3,000 gm
Steroid therapy Ritodrine therapy	24 24	5.1 ± 0.4* 2.2 ± 0.3*	3 5	3 6	21 (87.5%) 18 (75.0%)	2 3	4 7	19 14

<sup>\*</sup>The difference between the groups is significant (p < 0.001).

**Table V.** Results (mean  $\pm$  SEM) of the tocolytic therapy in women with a single fetus

		Gesatio	nal week	Birth
Group	No.	At therapy	At delivery	weight (gm)
Steroid therapy Ritodrine	23 24	$33.8 \pm 0.4$ $32.8 \pm 0.6$	39.1 ± 0.3 37.7 ± 0.4	3,460 ± 119 3,106 ± 118
therapy Significance of difference		NS	p < 0.01	p < 0.05

NS: Not significant.

the ritodrine group (two failures). Regular uterine contractions reappeared in four women receiving ritodrine within one week. Delivery occurred in all these women in spite of reinitiated ritodrine therapy. There was thus a 75.0% success rate in the ritodrine group and an 87.5% success rate in the steroid treatment group. The details of the failures are presented in Table III. The duration of premature labor was significantly shorter in the ritodrine-treated women than in those receiving steroids (Table IV). Ten women in the ritodrine group and six in the steroid treatment group gave birth to infants weighing less than 3,000 gm (Table IV). One infant in the steroid treatment group (the 900 gm B infant of twins) died of respiratory distress syndrome. The A twin survived but showed neurological disorders. All the other infants in this group had an Apgar score of 7 or more and had no complications. All the infants in the ritodrine group survived. One had an Apgar score of 4 at 1 minute and 6 at 5 minutes owing to an aspiration syndrome and also showed signs of mild cerebral lesions. Two others had transient postpartum asphyxia.

The mean birth weight of the infants and the mean gestational length in the singleton pregnancies were greater in the steroid treatment group than in the ritodrine group (Table V). The number of days gained after the therapy  $(38.1\pm4.3)$  was not significantly greater in the steroid group than in the ritodrine group  $(35.9\pm5.7)$ . This may be due to the fact that steroid treatment was initiated in women with an approximately 1-week-longer gestational time compared to those in the ritodrine group. The significances of the differences in the results remain unchanged, even if the four cases in both groups with induced delivery at term are excluded.

**Endocrinologic results.** There were no significant differences between the groups in the initial serum values of P,  $E_2$ ,  $E_3$ , or T (Table VI).

Both P and  $E_2$  displayed a rapid decline and  $E_3$  and T, a retarded decline from the initial level in the steroid treatment group (Fig. 1). The maximal decrease in the  $E_2$  level (about 60%) and in P,  $E_3$ , and T concentrations (about 30%) was observed on the first day after the initiation of therapy. The pretreatment levels of these hormones were achieved by the third or fourth day after commencement of the therapy.

<sup>†</sup>Died of respiratory distress syndrome.

Table VI. Steroid hormone levels (mean ± SEM) in the treatment groups before therapy.

Group	P (nmoles/L)	$E_{\pm}(nmoles/L)$	$E_3(nmoles/L)$	T (nmoles/L)
Steroid therapy (12)*	471 ± 33	$46.5 \pm 4.1$	$329 \pm 32$	$6.2 \pm 1.0$ $4.8 \pm 0.7$
Ritodrine therapy (13)*	386 ± 67	$61.3 \pm 8.1$	$282 \pm 49$	

<sup>\*</sup>Number.

The ritodrine group showed a significant fall in the serum level of  $E_2$  at 3 hours, whereas the P,  $E_3$ , and T concentrations did not change (Fig. 1).

#### Comment

The present study employs a new modification of hormonal therapy for the suppression of uterine activity in preterm labor, a combination of cortisol and 17 OHP-C. This combined treatment was at least as effective as a widely used therapy with ritodrine. The initial success rate of about 92% and the inhibition of premature labor for at least 1 week in 75% of the ritodrinetreated cases closely corresponds to previous observations.10 The simultaneous administration of progestin and glucocorticoid may have a dual inhibitory effect on uterine contractions: a direct suppressive action on the myometrial cells and an indirect action through inhibition of synthesis and activation of catabolism of prostaglandins (PGs). At the cellular and subcellular level, 17 OHP-C may favor the hyperpolarizing effects of P on myometrial sarcolemma and decrease the free calcium concentration within the cells,12 thus promoting relaxation of the uterus. A crucial step in the synthesis of PGs is the release of the lysosomal enzyme phospholipase A2, which specifically removes PG precursor acids, thus providing substrate for the formation of PGs. Glucocorticoids are able to arrest the release from phospholipids of the fatty acid substrate required for PG synthesis. This effect is caused through induction of the biosynthesis of a factor which acts as a phospholipase A2 inhibitor.13 Many animal experiments point to the P-to-E2 balance as an important regulator of PG synthesis and catabolism. A decrease in P and a rise in E2 in the blood possibly induce the decidual lysosomes to become labile.14 Our medication counteracts this alteration in the P-to-E2 balance. The enzyme PG dehydrogenase (PGDH) catalyzes the catabolism of PGs. In animal experiments, treatment with P was followed by an increase in PGDH, whereas E2 reduced PGDH activity.15 Our treatment regimen might thus enhance the activity of PGDH and consequently reduce PG concentration. A retarded suppressive effect of the steroid treatment on uterine contractions is in good accord with the assumption that this therapy mainly acts by modifying the metabolism of PGs and only secondarily by direct action on the myometrial

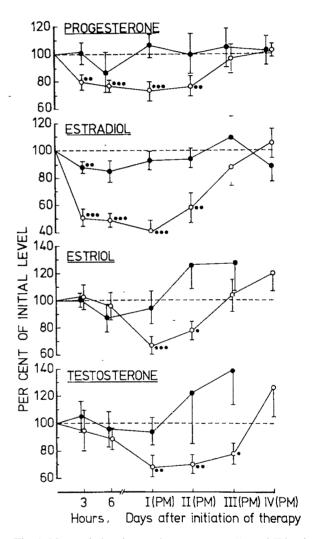


Fig. 1. Mean relative changes in serum P,  $E_2$ ,  $E_3$ , and T levels compared with pretreatment values in patients treated with a combination of cortisol and 17 OHP-C (o—o), or with rito-drine alone (•—•). The significances of the differences from the pretreatment level are indicated by asterisks. \*P < 0.05. \*\*P < 0.01. \*\*\*P < 0.001.

rells. The fetoplacental synthesis of E<sub>2</sub> and E<sub>3</sub> was reduced in our patients, as also noted previously after maternal glucocorticoid treatment.<sup>7</sup> This is due to a decrease in the supply of dehydroepiandrosterone sulfate from both fetal and maternal adrenals. The platental synthesis of P is independent of the administration of cortisol. The decline in the serum P level by

about 30% found in this study is thus likely to be associated with the administration of 17 OHP-C. This might inhibit those placental enzymes which convert cholesterol to P. This hypothesis is indirectly supported by observations in vitro, which demonstrated that the conversion of pregnenolone to P in the tissue of corpora lutea of early pregnancy was markedly inhibited by different progestins. <sup>16</sup> The decrease in the serum P level could also be due to activation of the liver enzymes responsible for P metabolism. These enzymes can be artificially induced and synthetic progestogens are po-

tent inducers of various enzymes. The hormonal changes observed were of short duration and did not disturb fetal well-being. The use of 17 OHP-C during late pregnancy is not considered hazardous with regard to either masculinization of the female fetus or development of malformations.<sup>8</sup>

A combination therapy with cortisol and 17 OHP-C results in a shift in the P-to-E<sub>2</sub> balance to P dominance. This change seems to have suppressive action on premature labor.

#### REFERENCES

- 1. Csapo, A. I.: The onset of labor, Lancet 2:227, 1961.
- Pinto, R. M., Fish, L., Schwarz, R., and Montiori, E.: Action of oestradiol-17β upon uterine contractility and the milkejecting effect in the pregnant women, Am. J. Obstet. Gynecol. 90:99, 1964.
- Turnbull, A. C., Pattern, P. T., Flint, A. P. F., Keirse, M. J. N. C., Jeremy, J. Y., and Anderson, A. B. M.: Significant fall in progesterones and rise in oestradiol levels in human peripheral plasma before onset of labor, Lancet 1:101, 1974.
- Sybulksi, S., and Mauchan, G. B.: Maternal plasma estradiol levels in normal and complicated pregnancies, Am. J. Obstet. Gynecol. 113:310, 1972.
- Fuchs, F., and Stakemann, G.: Treatment of threatened premature labor with large doses of progesterone, Am. J. OBSTET. GYNECOL. 79:172, 1960.
- Brenner, W. E., and Hendricks, C. H.: Effect of medroxyprogesterone acetate upon the duration and characteristics of human gestation and labor, Am. J. Obstet. Gynecol. 83:1094, 1962.
- Whitt, G. G., Buster, J. E., Killam, A. P., and Scragg, W. H.: A comparison of two glucocorticoid regimens for acceleration of fetal lung maturation in premature labor, Am. J. Obstet. Gynecol. 124:479, 1976.
- Johnson, J. W. C., Austin, K. L., Jones, G. S., Davis, G. H., and King, T. M.: Efficacy of 17α-hydroxyprogesterone caproate in the prevention of premature lapor, N. Engl. J. Med. 293:675, 1975.
- Zuspan, F. P., Cordero, L., and Semchyshyn, S.: Effects of hydrocortisone on lecithin-sphingomyelin ratio, Ам. J. Obstet. Gynecol. 128:571, 1977.

- 10. Baumgarten, K.: Results of tocolysis in threatened premature labor, *in* Bombiani, A., Cosmi, E. V., Fischetti, B., et al., editors: Recent Advances of Beta-Mimetic Drugs in Obstetrics, Rome, 1977, Sociata Editrice Universo, pp. 71-91
- 11. Hammond, G. L., Viinikka, L., and Vihko, R.: Automation of radioimmunoassays for some sex steroids with use of both iodinated and tritiated ligands, Clin. Chem. 23:1250, 1977.
- Csapo, A.: The effects of oxytocic substances on the excitability of the uterus, in Caldeyro-Barcia, R., and Heller, H., editors: Proceedings of the Montevideo International Symposium on Oxytocin, New York, 1959, Pergamon Press, pp. 100-123.
- Flower, R. I., and Blackwell, G. I.: Anti-inflammatory steroids induce biosynthesis of a phospholipase A<sub>2</sub> inhibitor which prevents prostaglandin generation, Nature 270: 456, 1979.
- 14. Gustawii, B.: Release of lysosomal acid phosphatase into the cytoplasm of decidual cells before the onset of labor in humans, Br. J. Obstet. Gynaecol. 82:177, 1975.
  15. Flower, R. I.: The role of prostaglandins in parturition
- 15. Flower, R. I.: The role of prostaglandins in parturition with special reference to the rat, in The Fetus and Birth, Ciba Foundation Symposium, Amsterdam, 1977, Excerpta Medica, vol. 47, pp. 297-312.
- cerpta Medica, vol. 47, pp. 297-312.

  16. Saure, A., Karjalainen, O., and Teräväinen, T.: The effect of synthetic gestagens on progesterone formation in vitro in human corpus luteum of early pregnancy, Eur. J. Obstet. Gynaecol. Reprod. Biol. 6:223, 1976.

#### Pregnancy and systemic lupus erythematosus

MARK T. HOUSER, M.D.
ALFRED J. FISH, M.D.
GEORGE E. TAGATZ, M.D.
PRESTON P. WILLIAMS, M.D.
ALFRED F. MICHAEL, M.D.
Minneatolis, Minnesota

Eleven patients with 18 pregnancies occurring during the course of systemic lupus erythematosus (SLE) were reviewed. Ten had long-standing lupus glomerulonephritis and a single patient developed glomerulonephritis during pregnancy. Patients were divided into those without (Group A) and those with (Group B) clinical evidence of renal disease or active SLE at conception. In Group A there were 10 pregnancies in five patients; all pregnancies were uncomplicated, except for mild superimposed pre-eclampsia in two, and all resulted in term delivery. Eight pregnancies in six patients occurred in Group B; four pregnancies were complicated by severe (2) or mild (1) superimposed pre-eclampsia and the onset of glomerulonephritis (1), resulting in three premature deliveries and a spontaneous abortion. The remaining four pregnancies were uncomplicated but resulted in one term delivery, one elective abortion, and two spontaneous abortions. None of the patients developed either renal failure or a rapidly progress ve course following pregnancy. (AM. J. Obstet. Gynecol. 138:409, 1980.)

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) usually occurs in female subjects during the second, third, and fourth decades of life. Consequently, the advisability of pregnancy is one of the difficult decisions confronting many of these patients and their physicians. Published reports have generally described an unpredictable maternal course during pregnancy with high rates of fetal wastage and exacerbation of SLE during the postpartum period. These complications have been particularly severe in patients with lupus nephritis. Recently, we described a group of patients with lupus erythematosus (LE) occurring within the first two decades of life. We now report our experience with pregnancy in this well-defined population.

#### Material and methods

**Population.** Eighteen pregnancies in 11 patients, occurring between August, 1966, and November, 1979,

From the Departments of Pediatrics and Obstetrics and , Gynecology, University of Minnesota Medical School. Supported in part by Grant AI 10704 from the National Institutes of Health.

Received for publication March 17, 1980.

Revised July 3, 1980.

Accepted July 21, 1980.

Reprint requests: Alfred F. Michael, M.D., Department of Pediatrics, Box 491, Mayo Memorial Building, University of Minnesota Hospitals, Minneapolis, Minnesota 55455.

**Table I.** Summary of renal disease and therapy during the initial course 5 to 17 years prior to pregnancy

Case no.	Lupus nephritis†	Rena! histology score†	Clinical rena! disease‡	Initial therapy§
1 (12*)	DP	Severe	Severe	Р, А
2 (5)	MES	Severe	Severe	P, A
3 (1)	MES	Moderate	Severe	C
4 (10)	FP	Severe	Severe	P, A
5 (15)	. <b>DP</b>	Severe	Severe	P, A
6 (9)	DP	Severe	Severe	P, A
7 (16)	MEM	Severe	Severe	P, A
8 (18)	MEM	Moderate	Moderate	P, A, Cy
9 (41)	MES	Moderate	Moderate	P, A
10 (17)	MES	Moderate	Severe	P, A
11	_		None	S

\*Numbers in parentheses refer to patient identification numbers in a previous publication.<sup>2</sup>

†Morphologic classification of the most abnormal biopsy at any time during this period. PP = Diffuse proliferative lupus nephritis; FP = focal proliferative lupus nephritis; MES = mesangial lupus nephritis; MEM = membranous lupus nephritis.

‡Based on lowest GFR and/or highest level of protein excretion at any time during this period. Severe = GFR < 65 ml/min/1.73 sq m and/or urinary protein excretion >2.5 mg/24 hours. Moderate = GFR 66 to 90 ml/min/1.73 sq m and/or urinary protein excretion 0.2 to 2.4 gm/24 hours.

C = Cortisone; C =

Table II. Summarization of course during pregnancy and post partum

		Prepreg	nancy†			Preg	gnancy	
Case No.*	Duration lupus (yr)	Clinical activity‡	Clinical renal disease§	Therapy <sup>  </sup> (mg)	Clinically active lupus	Clinical renal disease	Superimposed pre-eclampsia	Duration of gestation
roup A: P	atients with no ev	ridence of clinic	al renal diseas	se or clinical acti	vity of SLE at the	onset of pregn	апсу	
ı (Î2)	9	Ŏ	0	P 20 QOD	0	0.	0	Term
)	1 I	0	0	P 15 QOD	0	0	0	Term
(5)	12	0	O	P 30 QOD	0	0	0	Term
	15	0	0	P 30 QOD	0	0	0	Term
(1)	8	0	C	C 100 QD	0	0	0	Term
	10	0	C	C 50 QD	0 .	0	0	Term
(10)	12	0	0	None	. 0	0	0	Term
	13	0	0	None	0	0	0	Term
(15)	5	0	C	P 20 QOD	0	Mod.	Mild	Term
	7	0	0	P 20 QOD	0	Mod.	Mild	Term
oup B: P	atients with evide	ence of clinical	renal discase o	r clinical activity	of SLE at the ons	et of pregnant	<b>7</b> y	
(9) <sup>*</sup>	17	+	0	P 75 QOD A 125 QD	+	0	0	Term
(16)	7	+	Sev.	P 25 QOD	+	Sev.	Sev.	35 wk C-section
(18)	6	0	Mod.	P 25 QOD	0	Mod.	0	12 wk E-abortion
)	9	0	Mod.	P 25 QOD	0	Mod.	0	10 wk S-abortion
(41)	10	0	Mod.	P 25 QOD	0	Mod.	Sev.	20 wk S-abortion
a (17)	9	+	Mod.	P 25 QOD A 50 QD	+	Mod.	0	10 wk S-abortion
b	10	+	Mod.	P 20 QOD A 50 QD	+	Mod.	Mild	34 wk
l	10	+	0	s	+	Sev.	0	36 wk C-section

Abbreviations: Cesarean section (C-section); elective abortion (E-abortion); spontaneous abortion (S-abortion); respiratory distress syndrome (RDS); every other day (QOD).

were reviewed. Fifteen pregnancies in nine patients were managed by us prior to and throughout gestation. One patient (Case 11) was first seen in the third trimester coincident with the onset of lupus glomerulone-phritis and one patient (Case 4) had two pregnancies occurring 3 and 4 years after leaving our care.

Table I summarizes the renal histology, the severity of the clinical renal disease, and the therapy during the initial course of LE that occurred 5 to 17 years prior to pregnancy. Clinical renal disease, documented by changes in glomerular filtration rate (GFR) and proteinuria, was evident in 10 patients (Cases 1 to 10) at some time during this period. All patients had active, multisystem LE; 10 patients (Cases 1 to 10) received steroids, and all but two patients (Cases 3 and 11) received azathioprine and/or cyclophosphamide as part of their initial therapy.

Serologic evaluation. Multiple serologic determina-

tions were done on all patients during the course of LE. These included measurements of C3, CH50, and fluorescent antinuclear antibodies, as previously described.<sup>2</sup> In addition, sera maintained at  $-70^{\circ}$  C were available from 12 pregnancies. In 11, the nearest specimen obtained prior to the onset of pregnancy (1 week to 5 months) was examined retrospectively for immune complexes by the solid and fluid phase C1q binding assays<sup>3</sup>. <sup>4</sup> and for antinative deoxyribonucleic acid (anti-nDNA) antibody by the Crithidia luciliae assay.<sup>5</sup> In one pregnancy, the earliest available serum following conception was examined (4 months).

Clinical activity. Clinical activity of SLE was defined as the composite of symptomatology, serology, and requirement for immunosuppressive therapy. Patients considered to have no clinical activity had absent or minimal symptomatology, which was readily controlled with low-dose steroid therapy, and on serologic exami-

<sup>\*</sup>Numbers in parentheses refer to patient identification numbers in a previous publication.2

<sup>†</sup>Refers to patient's status during 6-month period prior to pregnancy.

<sup>‡</sup>Clinical activity of SLE, renal disease, and presence of toxemia indicated as absent (0), present (+), moderate (Mod.), and severe (Sev.).

<sup>§</sup>Based on glomerular filtration rate and urinary protein excretion (see text or Table 1).

<sup>&</sup>quot;Therapy shown as prednisone (P), azathioprine (A), cortisone (C), and salicylates (S).

Postpar	rtum			Infants	
Clinically active lupus	Clinical renal disease	Sex	Weight	Apgar Score (1 min15 min)	Neonatal course
0	0	F	3,050	9/9	Benign
+	0	M	3,200	-	Benign
0	0	M	3,290	6/9 .	Benign
0	0	F	2,750	6/7	Benign
, 0	0	M	3,000	9/10	Benign
0	0	M	3,470	8/10	Benign
0	0	F	3,100	8/9	Benign
0	0	F	3,685	8/9	Benign
0	0	F	2,200	8/9	Benign
+	0	M	2,250	6/9	Benign
+	0	M	2,850	9/9	Benign
+	Sev.	M	2,350	5/7	Mild RDS
′ 0	Mod.				
0	Mod.				
0	Mod.				
+	Mod.				
+	Mod.	F	1,540	7/8	Benign
+	Mod.	M	2,530	7/8	Benign .

nation had normal levels of C3, CH50, and C1q binding activity and had no anti-nDNA antibody. Patients designated as having clinically active SLE displayed single-system or multisystem symptomatology, exhibited serologic evidence of activity with hypocomplementemia, circulating immune complexes, and anti-nDNA antibody, or required treatment with high-dose prednisone and azathioprine to suppress disease activity.

Renal disease. Impairment of renal function was clinically assessed as previously described. A diagnosis of severe clinical renal disease was made if the patient demonstrated a GFR of less than 65 ml/min/1.73 sq m and/or urinary protein excretion greater than 2.4 gm/24 hours; moderate clinical renal disease was classified as a GFR of 66 to 90 ml/min/1.73 sq m and/or urinary protein excretion of 0.2 to 2.4 gm/24 hours, and no clinical renal disease was classified as a GFR of greater than 90 ml/min/1.73 sq m and no proteinuria.

#### Results

Patients were divided into two groups, those without (A) and those with (B) evidence of clinical renal disease and/or clinical activity of SLE in the immediate prepregnancy period (Table II). Duration of SLE was 5 to 17 years (mean 10 years) prior to conception.

**Prepregnancy period.** Five patients (Cases 1 to 5) had neither clinical renal disease nor active SLE in the immediate period antedating pregnancy. One patient (Case 2) had low-titer anti-nDNA antibody but was included in Group B because of a long-standing asymptomatic course and a lack of other serologic parameters of active SLE.

Six patients (Cases 6 to 11) had evidence of clinical renal disease and/or active SLE in the immediate prepregnancy period. Four patients (Cases 7 to 10) had clinical renal disease; two patients (Cases 7 and 8) had membranous lupus nephritis with severe and moderate clinical renal disease, respectively, and two patients (Cases 9 and 10) had mesangial lupus nephritis and moderate clinical renal disease. Four patients (Cases 6, 7, 10, and 11) had active SLE; three patients (Cases 6, 10, and 11) had symptomatic arthritis, one patient (Case 7) exhibited severe lupus dermatitis, and one patient (Case 11) also had seizures. On serologic testing, three patients (Cases 6, 10, and 11) demonstrated hypocomplementemia, one patient (Case 6) had circulating immune complexes, and one patient (Case 7) showed high-titer anti-nDNA antibody.

Hypertension was present only in Case 7 prior to pregnancy and it was readily controllable with thiazide diuretics and methyldopa.

Pregnancy and delivery. A change in clinical renal disease and/or clinical activity of SLE occurred in five patients (Cases 5, 7, 9, 10, and 11) during pregnancy. Four patients (Cases 5, 7, 9, and 10) developed superimposed pre-eclampsia. Two patients (Cases 5 and 10) developed mild hypertension and proteinuria, which did not effect the obstetric course of either pregnancy in Case 5 and were associated with premature labor during the second pregnancy in Case 10. Severe hypertension and proteinuria developed in the other two patients with superimposed pre-eclampsia and resulted in early cesarean section (Case 7) and a spontaneous abortion (Case 9). Only one patient (Case 11) exhibited a change in the clinical activity of SLE. She had a severe, acute exacerbation in the third trimester associated with the development of severe clinical renal disease. Following early cesarean section and improvement with high-dose prednisone, a renal biopsy was performed in the postpartum period which demonstrated focal proliferative lupus nephritis. None of the other patients had any changes in therapy during gestation. All except one (Case 3) were treated with high-dose daily parenteral steroids at the time of delivery with subsequent tapering to baseline after 2 to 4

All offspring of patients in Group A were delivered at term and had a benign neonatal course (Table II).

Of the pregnancies in Group B, only one resulted in term delivery. Severe superimposed pre-eclampsia and lupus nephritis necessitated premature delivery by cesarean section in two patients and mild superimposed pre-eclampsia was associated with spontaneous premature delivery in one patient. There was one elective abortion for nonmedical reasons, and three spontaneous abortions occurred. There were no perinatal deaths and only one infant (in Case 7) had mild respiratory distress syndrome. Only one congenital anomaly was recognized in this population as the infant in Case 11 had a unilateral multicystic, dysplastic kidney. In all pregnancies, term delivery occurred in 61%; premature delivery, in 16.6%; and spontaneous abortion in 16.6%.

Postpartum period and follow-up. Changes in clinical renal disease and/or clinical activity of SLE occurred in seven patients (Cases 1, 5, 6, 7, 9, 10, and 11) during the postpartum period. Improvement in clinical renal disease occurred in all five patients (Cases 5, 7, 9, 10, and 11) who had deterioration of renal function during pregnancy. Four patients (Cases 5, 7, 9, and 10) returned to their prepregnancy state following delivery and one patient (Case 11) was improved with steroid therapy. Four patients (Cases 1, 5, 6, and 11) demonstrated changes in clinical activity. Two patients (Cases 1 and 5) in Group A developed mild arthritis without other symptoms or serologic abnormality following their second pregnancies. In each case, spontaneous resolution of symptoms occurred without a change in therapy. One patient (Case 6) had an intrauterine contraceptive device inserted following delivery and developed endometritis and a clinical exacerbation of SLE four months later. As such, this change in disease activity was probably unrelated to pregnancy.

In a follow-up of 4 months to 12 years (mean 4 years) there have been no deaths, no patient has developed end-stage renal failure, and none developed a rapidly progressive course following pregnancy.

#### Comment

The effect of pregnancy on SLE has been a subject of controversy and contradiction since the original report appeared in 1952.6 Most studies document high fetal wastage and prematurity associated with increased rates of exacerbation during gestation and in the postpartum period. In particular, patients with lupus nephritis seem to suffer high rates of fetal wastage and maternal morbidity and death although certainly favorable reports exist, especially in patients with inactive SLE prior to pregnancy. 7–13

It remains difficult, however to evaluate the risk for

any isolated pregnancy in patients with lupus nephropathy because of the incomplete documentation of clinical activity, serologic abnormalities, renal function, and therapy in most of the previously reported cases.

From a well-defined and unique population of patients who developed SLE during the first two decades of life, we characterized the clinical course of 18 pregnancies in 11 patients. All initially had active multisystem LE and 10 had documented pre-existing lupus nephropathy. The outcome clearly differentiated those without (Group A) and those with (Group B) evidence of active SLE and/or clinical renal disease prior to conception. In Group A, all but two pregnancies were uncomplicated; one patient had mild superimposed preeclampsia during both of her pregnancies. In Group B there were four pregnancies complicated by mild (1) and severe (2) superimposed pre-eclampsia and the acute onset of lupus nephropathy (1), leading to a spontaneous premature delivery, one spontaneous abortion, and two other premature infants delivered by cesarean section. The remaining four pregnancies in this group were uncomplicated but resulted in one term delivery, one elective abortion, and two spontaneous first-trimester abortions. Maternal morbidity was low and there were no maternal deaths. Changes in renal functional status during gestation were noted only in those patients with superimposed pre-eclampsia and the single patient with active lupus nephritis. Following delivery, renal function returned spontaneously to prepregnancy status in the former patients and was improved with prednisone therapy in the latter patient. None of the patients developed renal failure or had a rapidly progressive course following pregnancy.

Fetal morbidity and mortality rates were also low. In all pregnancies, prematurity occurred in 16.6%, which is increased as compared to the incidence in the general population (8.6%, Minnesota Department of Health Statistics). Spontaneous abortions also occurred in 16.6% of all pregnancies, which is comparable to the quoted abortion rates in the general population of 15% to 22% of clinically recognized pregnancies. 14-16

In Group B, however, prematurity (37.5%) and spontaneous abortion (37.5%) occurred with a much higher than normal incidence. The single congenital anomaly, a unilateral multicystic, dysplastic kidney, occurred in the infant born to the only patient not receiving steroids during early embryogenesis.

We conclude that although pregnancy in patients with lupus nephropathy must be managed as a high-risk condition, the likelihood of unfavorable outcome in patients without abnormal renal function or active SLE seems small. However, patients with clinical renal

disease or evidence of active SLE are at higher risk for superimposed pre-eclampsia, spontaneous abortion, and prematurity although with intensive medical and obstetric management there appeared to be no longterm risk to maternal well-being.

We acknowledge the assistance of Drs. Barbara Burke and Jerome Dougan and Ms. Nancy Kirschling in preparing the manuscript.

#### REFERENCES

- Bulmash, J. M.: Systemic lupus erythematosus and pregnancy, Obstet. Gynecol. Annu. 7:174, 1978.
- Fish, A. J., Blau, E. B., Westberg, N. G., Burke, B. A., Vernier, R. L., and Michael, A. F.: Systemic lupus erythematosus within the first two decades of life, Am. J. Med. 62:99, 1977.
- 3. Tung, K. S. K., Woodroffe, A. J., Ahlin, T D., Williams, R. C., and Wilson, C. B.: Application of the solid phase Clq and Raji cell radioimmunoassays for the detection of circulating immune complexes in glomerulonephritis, J. Clin. Invest. 62:61, 1978.
- Zubler, R. H., and Lambert, P. H.: The <sup>125</sup>I-Clq binding test for the detection of soluble immune complexes, in Bloom, B. R., and David, J. R., editors: In Vitro Methods in Cell Mediated and Tumor Immunity, New York, 1976, Academic Press. Inc., p. 565.
- Academic Press, Inc., p. 565.

  5. Sontheimer, R. D., and Gilliam, J. N.: An immunofluorescence assay for double-stranded DNA antibody using Crithidia luciliae kinetoplast as a double-stranded DNA substrate, J. Lab. Clin. Med. 91:550, 1978.
- Donaldson, L. B.: Lupus erythematosus in pregnancy, West. J. Surg. 60:579, 1952.
- Garenstein, M., Pollak, V. E., and Kark, R. M.: Systemic lupus erythematosus and pregnancy, N. Engl. J. Med. 267:165, 1962.
- 8. Bear, R.: Pregnancy and lupus nephritis: A detailed report of six cases with a review of the literature, Obstet. Gynecol. 47:715, 1976.

- 9. Fraga, A., Mintz, G., Orozco, H. M., and Orozco, J.: Systemic lupus erythematosus: Fertility, pregnancy, fetal wastage and survival rate with treatment, a comparative study, Arthritis Rheum. 16:541, 1973.
- Strauch, B. S., and Hayslett, J. P.: Kidney disease and pregnancy, Br. Med. J. 4:578, 1974.
- Fainley, K. F., Whitworth, J. A., and Kincaid-Smith, P.: Glomerulonephritis and pregnancy, in Kincaid-Smith, P., Mathew T. H., and Becker, E. L., editors: Glomerulonephritis; Morphology, Natural History and Treatment, New York, 1973, John Wiley & Sons, Inc., p. 997.
- Cameron, J. S., Turner, D. R., Ogg, C. S., Williams, D. G., Lessof, M. H., Chantler, C., and Leibowitz, S.: Systemic lupus with nephritis: A long-term study, Q. J. Med. 189:1, 1979.
- Devoe, L. D., and Taylor, R. L.: Systemic lupus erythematosus in pregnancy, Am. J. Obstet. Gynecol. 135:473, 1979.
- Roth, D. B.: The frequency of spontaneous abortion, Int. J. Fertil. 8:431, 1963.
- Speroff, L., Glass; R. H., and Kase, N. G.: Clinical Gynecologic Endocrinology and Infertility, ed. 2, Baltimore, 1978. The Williams & Wilkins Co. p. 331
- 1978, The Williams & Wilkins Co., p. 331.
  16. Benirschke, K. T.: Cytogenetics, in Yen, S. S. C., and Jaffe, R. B., editors: Reproductive Endocrinology; Physiology, Pathophysiology and Clinical Management, Philadelphia, 1978, W. B. Saunders Co., p. 175.

## Uterine and ovarian artery blood flow in the rhesus monkey near term

M. MAURICE ABITBOL, M.D. EMERICK DEMETER, M.D. THIERRY BENAROSH

Jamaica, New York

Uterine and ovarian artery blood flow (UABF and OABF) were measured in six pregnant monkeys near term by means of the electromagnetic flowmeter. The average UABF was 21.4 ml/min and OABF was 1.9 ml/min. Complete aortic occlusion reduced UABF from 21.4 to 2.4 ml/min, while OABF increased from 1.9 to only 2.1 ml/min. In six pregnant monkeys near term, chronic partial constriction of the abdominal aorta for an average of 10 days produced a parallel reduction in UABF but no increased circulation through the ovarian or round ligament arteries. The ovarian arteries were not visualized on angiography in these pregnant monkeys even when the abdominal aorta was acutely or chronically constricted; the uterine arteries were readily seen. The authors concluded that acute or chronic aortic constriction in the pregnant monkey at term results in a noncompensated uterine blood flow (UBF) reduction. The possible implications in pregnant women are discussed. (AM. J. OBSTET. GYNECOL. 138:414, 1980.)

ALTHOUGH the most important pathway supplying blood to the uteroplacental unit is the uterine arteries, anastomotic circulation around these arteries is also crucial, especially when the abdominal aorta is compressed by the pregnant uterus. A major role has been attributed classically to the ovarian arteries as a secondary pathway for this anastomotic circulation. Many authors agree that this collateral circulation will be adequate when the abdominal aorta is compressed but others doubt it will be satisfactory all the time.

This collateral circulation has been studied experimentally by some. For instance, Misenheimer and associates<sup>5</sup> have chronically impaired uterine artery blood flow (UABF) in the pregnant rhesus monkey by applying nonexpandable bands around the uterine ar-

From the Departments of Obstetrics and Gynecology and Radiology, The Jamaica Hospital. The work was done at the I.R.M. Institute of the New York University School of Medicine, New York, Dr. F. E. Birkner, Director; Mario Clagnaz and Robert Kolwicz, Assistant Research Scientists.

Received for publication July 16, 1979.

Revised June 9, 1980.

Accepted June 30, 1980.

Reprint requests: M. Maurice Abitbol, M.D., Chairman, Department of Obstetrics and Gynecology, The Jamaica Hospital, 89th Ave. and Van Wyck Expressway, Jamaica, New York 11418.

teries before pregnancy. They demonstrated a marked reduction in placental blood flow with a 60% fetal death rate in the first pregnancy after UABF impairment. In a previous study by Abitbol and associates,4 uterine and ovarian artery blood flow (UABF and OABF) were measured in dogs by means of the electromagnetic flowmeter. In eight nonpregnant animals, UABF was, on the average, 3.2 ml/min and OABF was 0.4 ml/min. In 10 pregnant bitches near term UABF was 27.3 ml/min and OABF was 1.3 ml/min. Complete aortic occlusion in the pregnant bitch at term reduces UABF to 2.4 ml/min (loss of 24.9 ml/min) and increases OABF to only 1.6 ml/min (gain of 0.3 ml/min). It was concluded that most of the blood flow to the uteroplacental unit in the pregnant bitch was channeled through the uterine artery, and the marked drop in UABF produced by acute aortic occlusion is not compensated by an increase in OABF. The shortcoming of this study was that there are marked differences in the genital anatomy and physiology between women and the canine species, since in the latter the uterus is bicornuate and the placenta is labyrinthine and epitheliochorial. Besides, this was only an acute experiment with conditions much different from those in the woman, where collateral routes are gradually developed throughout pregnancy in response to progressive partial obstruction of the aorta by the growing uterus. 1. 6

To further investigate this collateral circulation, the

previous study was repeated on the rhesus monkey, whose genital anatomy and physiology are basically similar to those of humans. Still the relationships in the anthropoid pelvis of the monkey are somewhat different from those in the human pelvis; therefore, it may be difficult to produce a compression of the abdominal aorta by the pregnant uterus in this animal. For this reason, the abdominal aorta was approached directly in this new experiment; it was constricted acutely and also chronically in an attempt to study the collateral circulation under conditions closer to those existing in the pregnant woman.

#### Material and methods

A total of 12 pregnant and two nonpregnant rhesus monkeys (Macaca mulatta) were included in this study. Pregnancy in this primate lasts 168 days, and the fetus at term weighs 400 to 500 gm. All the pregnant monkeys were within the last 3 weeks of gestation; in three this was determined from the known date of conception and in the nine others, from the size of the pregnant uterus and the weight of the fetus at birth. The weight of these monkeys varied from 5.7 to 7.9 kg. Anesthesia was induced with phencyclidine hydrochloride,\* 1.5 to 2 mg/kg, injected subcutaneously 30 minutes before operation. This produced a satisfactory relaxation which lasted for up to 2 hours. When necessary, half of the initial dose was repeated 2 hours later. All the fetuses were alive as determined by palpation and/or fetal heart auscultation before operation.

The pregnant animals were divided into two groups of six each.

**Group 1.** The first group was used for an experiment on acute total constriction similar to the one previously described on the dog.4 After a laparotomy incision, a segment of the ovarian artery was exposed on each side lateral to the ovary and carefully dissected away from the surrounding structures. A 1 mm flow transducer was placed around it and fixed to the surrounding connective tissue to prevent any kinking. A flow transducer (1.5 or 2.5 mm, depending on the diameter of the vessel) was also placed around the uterine artery on each side. UABF and OABF, registered by the flow probes, were transmitted to a recording system which simultaneously registered the two UABF and the two OABF. The abdominal aorta was exposed extraperitoneally (to limit manipulation of the uterus) through a left paralumbar incision at a point just above the iliac bifurcation, and a vascular occluder was placed around it to produce occlusion on demand. UABF and OABF were studied when the abdominal aorta was completely

Table I. Femoral artery blood pressure on the monkey undergoing sham operation (in millimeters of mercury)

,	First sham operation		Second opera	
• !	Before	After	Before	After
First monkey Second monkey	117/74 106/62	109/71 110/65	120/80 100/65	121/78 100/65

In each instance, the blood pressure was recorded only after it had stabilized and presented minimal variations when taken three to four times consecutively.

Table II. UABF and OABF variations with acute aortic occlusion in the pregnant rhesus monkey (in milliliters per minute)

Monkey	Aortic	UA	BF	OA	Total	
No.	occlusion	Right	Left	Right	Left	UBF
1	No	32	26	2		60
	Yes	#0	#0	2.5		2.5
2	No	30	20	2	4	56
	Yes	3	4.5	2.5	4	14
3	No		29		2	
	Yes		2.5			
4	No	17	14	#0		31
	Yes	#0	4	#0		4
~ 5	No	18	20	2.5	2	42.5
	Yes	I	1.5	2.5	3	8
6	No	25	12	1	#0	38
	Yes	6	4	1.5	#0	11.5
Average	No	24.4	18.4	1.5	2	46.3
Ü	Yes	2.0	2.8	1.8	2.3	8.9
% Total						
olood flow	No	92.	4%	7.0	6%	100%
	Yes	10.	4%		8%	19.2%

released, then completely constricted for the purpose of determining if any increased circulation could occur in the ovarian arteries when the abdominal aorta is blocked. While the abdominal aorta was being occluded, then released, the different flows were continuously recorded by the flowmeter and on the strip recorder. The aorta was occluded two to six times on each animal, each occlusion lasting 1 to 10 minutes. The total of all occlusions in each animal lasted up to 30 minutes. There were minimal or no variations in the successive blood flow readings from one occlusion to the next and from one aortic release to the next. If a minimal difference was noted, the average value was taken. Because most of the operations performed on these animals were done extraperitoneally, and because the pregnant uterus was minimally manipulated through the small laparotomy incision, labor was not induced. No intra-amniotic catheter was inserted for fear of irritating the pregnant uterus. The blood flows

<sup>\*</sup>Sernylan, Parke Davis & Company, Detroit, Michigan.

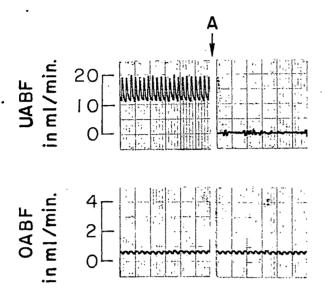


Fig. 1. Pregnant rhesus monkey at term. When aortic blood flow is suddenly interrupted (A), UABF becomes nil, while OABF presents no alteration.

were not measured when a rare uterine contraction occurred.

Group 2. The second group was used for an experiment on chronic partial constriction. In a first-stage operation, 6 the abdominal aorta of each animal was exposed extraperitoneally, as previously described. A 5 mm flow probe was placed around it, and then the abdominal aorta was constricted with a silk suture until approximately a 40% blood flow reduction had been produced and verified on the flowmeter. The silk suture was secured in that position, the flow probe was removed, and the incision was closed. The animal was returned to its cage. Five to 15 days later (the monkey was still pregnant) a laparotomy was performed and UABF and OABF were measured simultaneously by means of a technique similar to the one used in the first group. The silk suture around the aorta was then removed, and UABF and OABF were measured again simultaneously. The purpose of these manipulations was to determine if placing, then removing a chronic partial obstruction around the aorta during pregnancy could produce an increased collateral circulation through the ovarian arteries.

A third group, composed of two nonpregnant monkeys, was used as a control. First, the blood pressure in the hind limb of each animal was carefully recorded with an Arteriosonde 1010, after anesthesia induction, but before operation. Then a sham operation was performed as follows: the abdominal aorta was exposed extraperitoneally and a 5 mm flow probe was placed around it as in Group 2, but the silk suture around the

**Table III.** UABF and OABF in the pregnant rhesus monkey with, then without 40% chronic blood flow reduction of the abdominal aorta (in milliliters per minute)

M 1	Partial aortic	UAI	3 <i>F</i>	OA.		
Monkey No.	blood flow reduction	Right	Left	Right	Left	Total UBF
1	Present	15	7.5	2.5	3	28
	Relieved	24	12	2.5	1.5	40
2	Present	17	14.5	#0	2.5	34
	Relieved	18	15.5	#0	3.5	37
3	Present	21	17	1.5		39.5
	Relieved	33	26	2.5		61
4	Present	18			2	
	Relieved	30			2	
5	Present	10	12	#0	2 .	24
	Relieved	17	21	#0	2	40
Average	Present	15.8	12.8	1.0	2.4	32
Ŭ	Relieved	23	18.6	1.3	2.2	44.6
% Total	Present	64.	1%	7.6	%	71.7%
blood flow	Relieved	92.2%		7.8	100%	

aorta was placed so loosely that it barely reduced the aortic blood flow, if at all. The flow probe was removed, and the loose silk suture was left in. The incision was closed and the blood pressure in the hind leg was rechecked carefully before the animal was returned to its cage. One week later, the above steps were repeated in the reverse order; after anesthesia induction, the blood pressure in the hind leg was carefully recorded, the abdominal aorta was exposed, and the flow probe was placed around it. Then the loose silk suture and the flow probe were removed, the incision was closed, and finally the femoral blood pressure was checked in the hind leg. The purpose of this sham operation was to determine if the surgical manipulations were, by themselves, responsible for the aortic blood flow reduction. Had this been the case, the femoral blood pressure, which varies in relation to the aortic blood flow,7 would have shown a drop.

Arterial angiography was also performed in some of the animals in an attempt to visualize the ovarian and uterine arteries with and without occlusion of the abdominal aorta and to compare the diameters of these vessels under various conditions. A catheter introduced into the femoral artery was pushed into the abdominal aorta up to the level of the renal arteries. An automatic electric injector was used to inject 10 cc of 50% Hypaque into the aorta within 2 to 3 seconds.

Most of the animals from the two groups were killed either at the end of the experiment or a few days later. Then ovarian and uterine arteries were resected. The fresh tissue was immediately examined by low-power microscopy with a calibrated micrometer, and the inner diameters of these arteries were measured according to

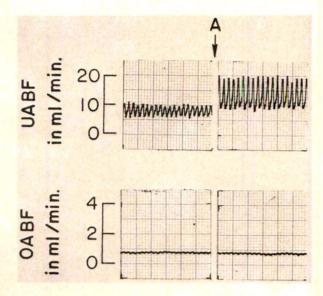


Fig. 2. Pregnant rhesus monkey near term with 40% aortic blood flow reduction of 9 days' duration. When aortic blood flow is suddenly re-established to normal (A), UABF doubles in value, while OABF presents no major alteration.

the technique previously described.4 The round ligament was also studied to determine if any important arterial structure could be seen in it.

The Gould-Statham portable blood flowmeter (SP 2202) together with the research model probes SP 2202R of various diameters and with the Statham strip chart recorder was used to measure the blood flow in the different arteries.7 All flow transducers are precalibrated in the factory. From time to time the calibration was checked in the animal laboratory by allowing heparinized blood from a monkey that had been killed to flow within an arterial segment around which the flow transducer was inserted. If the difference was more than 10%, the flow transducer was returned to the factory for recalibration.

Zero flow calibration was easily obtained by using the nonocclusive zero feature of this flowmeter. The zero flow was always determined first by producting a complete occlusion of the measured artery. This could not be done too often, however, because of the reactive hyperemia consequent to the occlusion, which always took a few minutes to clear up. But with the nonocclusive zero feature, the apparatus can be realigned to zero flow at any time without occluding the artery, and the meter and the recorder will indicate accurate blood flow measurements.

Vascular occluders Models VO 3 and VO 4 (Rhodes Medical Instruments) were used to produce a progressive and calibrated constriction of the abdominal aorta.

The systolic, diastolic, and mean blood flows were

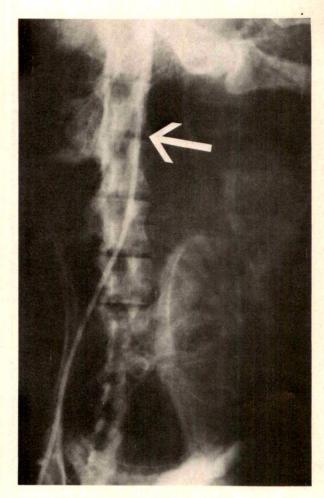


Fig. 3A. Pregnancy at term in rhesus monkey with an acute total aortic occlusion at the level of the second lumbar vertebra (arrow). No ovarian arteries are visualized.

recorded on each side, but only the mean flow will be reported here.

#### Results

In the animals undergoing sham operation, the aortic blood flow and the femoral blood pressure did not present any noticeable variations in the indicated values before and after the first procedure or before and after the second procedure (Table I). The conclusion that can be drawn from the study of this control group is that the manipulations associated with the surgical procedure are not responsible, by themselves, for any aortic blood flow reduction; the aortic constriction produced by the silk suture is the only factor responsible for the blood flow reduction observed in the pregnant groups.

Satisfactory blood flow measurements were recorded for the ovarian and uterine arteries in all the pregnant monkeys, at least on one side. The results of the acute

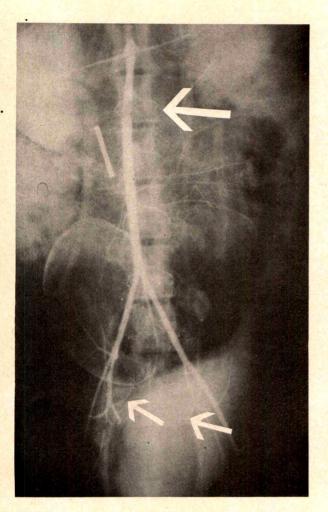


Fig. 3B. Pregnancy at term in rhesus monkey with partial aortic occlusion of 9 days' duration at L1 to L2 (large arrow). Uterine arteries are easily visualized (small arrows) but no ovarian arteries are seen.

total aortic occlusion are recorded in Table II, and in Table III those of chronic partial occlusion are presented. In some instances, a pulsatile flow was seen easily on the biphasic recording, but on the mean flow it was so small that it was considered to be near zero.

In the first group, UABF varied from 12 to 32 ml/min with an average of 21.4 ml/min, and OABF varied from 0 to 4 ml/min with an average of 1.9 ml/ min. The total uterine blood flow (UBF) reported here includes only the blood coming from the two uterine and the two ovarian arteries. By applying the formula UBF = 2 UABF + 2 OABF, UBF in the pregnant monkey varied from 31 to 60 ml/min, with an average of 46.3 ml/min. The ovarian artery contributes 7.6% and the uterine artery 92.4% of the blood flow to the uteroplacental unit in the monkey at term (Table II). When the abdominal aorta was acutely and completely constricted (Fig. 1), UABF dropped to zero or near

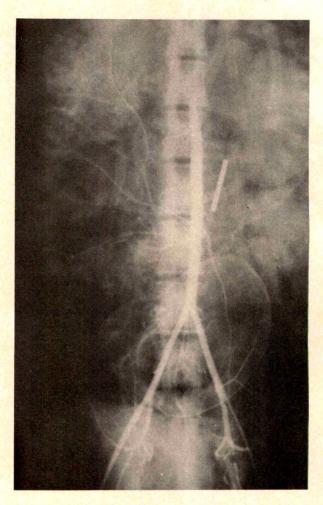


Fig. 3C. The partial occlusion of the pregnant monkey represented in Fig. 3B has been removed. The entire arterial system of the pelvis is well visualized. No ovarian arteries are

zero in all cases, and OABF presented no noticeable variation.

After more than 2 hours of surgical experimentation with repeat episodes of aortic constriction, fetal bradycardia, then fetal death occurred in three cases. The other three fetuses were delivered through a hysterotomy incision at the end of the experiment; one was compromised and died shortly afterward, and the other two appeared to be healthy.

In the second group, where aortic blood flow had been chronically reduced by 40%, one monkey experienced a stillbirth 4 days after operation. UABF and OABF were measured in the other five monkeys with living fetuses. The average UABF was 14.3 ml/min and the average OABF was 1.7 ml/min (Table III). Here, too, the total UBF, determined by the aforementioned formula, was 32 ml/min. The silk suture around the abdominal aorta was removed, and 15 to 30 minutes

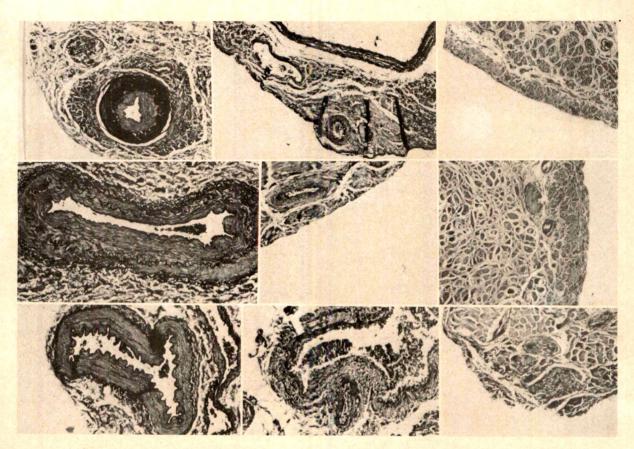


Fig. 4. Nonpregnant rhesus monkey (top), pregnancy at term (middle), and pregnancy near term with 40% aortic blood flow reduction of 9 days' duration (bottom). The uterine artery (left) has markedly hypertrophied during pregnancy. There is no noticeable ovarian artery hypertrophy (middle), even with partial aortic occlusion. In the round ligament (right), only small vascular structures can be recognized. (Verhoeff elastic stain, after formalin fixation. Original magnification ×60.)

later UABF and OABF were measured again. UABF jumped from an average of 14.3 ml/min to an average of 20.8 ml/min, while OABF presented no noticeable changes (Fig. 2).

Arterial angiography was successful in four pregnant monkeys. The uterine arteries were easily visualized in all of them. No ovarian or round ligament arteries could be seen in spite of a total aortic constriction lasting up to 30 minutes or a partial aortic obstruction lasting up to 15 days (Figs. 3A, 3B, and 3C). It is puzzling that the ovarian artery could not be visualized on angiography in the pregnant monkey as it had been visualized in the pregnant dog, where an identical technique was used.4 To our knowledge, however, in no other investigation has the ovarian artery of the monkey ever been visualized by angiography.

In fresh tissues, the average inner diameter of the ovarian artery was 0.2 mm and that of the uterine artery was 1.1 mm. Acute or chronic aortic constriction did not appear to produce any variation in the diame-

ter of the ovarian arteries. No arterial structures of any significance could be found in the round ligament or within its vicinity (Fig. 4).

#### Comment

While UABF was rather easy to measure because of the relatively large size of the uterine artery, OABF, on the other hand, was difficult to register. Because of its small diameter, the ovarian artery was difficult to expose, was easily traumatized, and frequently became occluded. Bilateral OABF measurements were possible in only half of the cases. Even in those cases where recording was possible, reservation should be made about the significance of the absolute values of OABF. It is usually very difficult to accurately measure flows in the magnitude of 1 ml per minute. However, the problems that the authors address themselves to in this research are first, to establish the fact that OABF is minimal, and second, to ascertain that when UABF is interrupted the ovarian arteries do not automatically

open up to accommodate an amount of blood flow similar to UABF. These two facts were easily established here

OABF appears to be slightly higher in the pregnant monkey (7.6%) than in the pregnant dog (4.7%), but in both animals it seems to be very low. In four of five monkeys from the second group it is remarkable to notice that UABF reduction resulting from the partial aortic constriction remained reduced for as long as the aorta was constricted and immediately returned to normal as soon as the aortic constriction was removed. In the fifth monkey, the removal of this aortic stricture resulted only in a minimal UABF variation (Animal 2, Table III). In this animal, it is possible that the surgical manipulation resulted in an aortic spasm which spontaneously corrected itself shortly afterwards.

Only UABF and OABF were considered here when total UBF was calculated. Of course other arteries such as vaginal and round ligament arteries1 also contribute to the blood supply of the pregnant uterus, but this contribution must be minimal because with the technique used UBF varied from 31 to 60 ml/min. These figures are only slightly lower than those reported on the rhesus monkey at term by other investigators. Meschia and associates,8 using methods based on the Fick principle, reported 28.6 to 68.2 ml/min. Using microspheres on slightly larger monkeys, Novy and associates9 reported values varying from 39.61 to 127.41 ml/min. Assali and associates<sup>10</sup> directly measured UBF in early human pregnancy and found a blood flow of 56.7 ml/min at 12 weeks' gestation (estimated total uterine weight of 593 gm). Since the total uterine weight of the rhesus monkey at term varies between 600 and 700 gm, one can conclude that for an equal total uterine weight, humans and subhumans have approximately the same UBF. Since the figures based on the Fick principle<sup>8</sup> and on microspheres<sup>9</sup> are higher than those given by the flowmeter, one can speculate on the existence of other sources of blood supply to the pregnant uterus besides UABF and OABF. The contribution of these sources is certainly lower than the one coming from the uterine arteries, which remain the main source of blood supply to the pregnant

The conclusions to be drawn from the present experiments in the pregnant rhesus monkey are as follows:

1. The majority of the blood to be uteroplacental

unit is channeled through the uterine arteries, and the contribution of the ovarian arteries or any other known arteries is minimal.

- 2. When the abdominal aorta is suddenly and totally occluded, UABF is totally or almost totally interrupted, while there is no apparent increase in OABF.
- 3. A partial reduction in aortic blood flow lasting 5 to 15 days produces a parallel reduction in UABF, which remains reduced for the same length of time. This UABF is corrected as soon as the aortic constriction is removed.

In the pregnant monkey there does not appear to be any satisfactory collateral circulation when the abdominal aorta is acutely or chronically occluded. At least no collateral circulation develops through the ovarian or the round ligament arteries. This aortic occlusion sometimes appears to be dangerous to the fetus since it resulted in fetal damage in four of six monkeys with acute occlusion and one of six with chronic occlusion. Misenheimer and associates<sup>5</sup> came to similar conclusions in their series and, remarkably, demonstrated an improved collateral circulation in subsequent pregnancies.

Is it possible to extrapolate the present results to pregnant women, in view of the similarity in reproductive biology between nonhuman and human primates? In pregnant women severe aortic compression by the pregnant uterus in the supine position, especially during uterine contraction, is well known and has been reported in the medical literature. 11. 12 When this occurs, the blood supply is not channeled through the uterine arteries in sufficient quantity, but the ovarian arteries show a compensatory circulation which seems to be radiologically satisfactory in some cases. There are other cases, however, where on x-ray film the ovarian circulation is deficient or even absent. 1-4, 13 This may be caused by either a lack of compensatory ovarian widening or by simultaneous compression of the ovarian arteries by the pregnant uterus.1, 2 Possibly the uteroplacental unit then will be faced with diminished and insufficient blood flow and placental insufficiency and ischemia may develop.14

The experimental research presented here brings forward the concept that compression of the abdominal aorta by the pregnant uterus may not always be such a benign condition. Further studies in this direction are in order.

#### REFERENCES

- Bieniarz, J., Yoshida, T., Romero-Salinas, G., Curuchet, E., Caldeyro-Barcia, R., and Crottogini, J. J.: Aortocaval compression by the uterus in late human pregnancy. IV:
- Circulatory homeostasis by preferential perfusion of the placenta, Am. J. Obstet. Gynecol. 103:9, 1969.
- 2. Borell, U. and Fernstrom, I.: The ovarian artery. An ar

- teriographic study in human subjects, Acta Radiol. (Diagn.) (Stockh.) 42:253, 1954.
- 3. Abitbol, M. M.: Aortic compression by pregnant uterus, N. Y. State J. Med. 76:1470, 1976.
- 4. Abitbol, M. M., Demeter, E., and Benarosh, T.: Uterine and ovarian artery blood flow in the pregnant dog. Attempt at comparative study in pregnant women, Am. J. OBSTET. GYNECOL. 136:780, 1980.
- 5. Misenheimer, H. R., Ramsey, E. M., Martin, C. B., Jr., et al.: Chronically impaired uterine artery blood flow, Obstet. Gynecol. 35:415, 1970.
- 6. Abitbol, M. M., Ober, W. B., Gallo, G. R., et al.: Experimental toxemia of pregnancy in the monkey. With a preliminary report on renin and aldosterone, Am. J. Pathol. 86:573, 1977.
- 7. Gordon, A. S.: Practical Aspects of Blood Flow Measurements, Statham Instruments, Inc., Oxnard, Califor-
- 8. Meschia, G., Behrman, R. E., Hellegers, A. E., Schruefer, J. J., Battaglia, F. C., and Barton, D. H.: Uterine blood flow in the pregnant rhesus monkey, Am. J. OBSTET. GYNECOL. 97:1, 1967.
- 9. Novy, M. J., Thomas, C. L., and Lees, M. H.: Uterine

- contractility and regional blood flow responses to oxytocin and prostaglandin E in pregnant rhesus monkeys, AM. J. OBSTET. GYNECOL. 122:419, 1975.
- 10. Assali, N. S., Ronramo, L., and Peltonen, J.: Measurement of uterine blood flow and uterine metabolism. VIII. Uterine and fetal blood flow and oxygen consumption in early human pregnancy, Am. J. Obstet. Gynecol. 79:86, 1960
- 11. Bieniarz, J., Crottogini, J. J., Curuchet, E., Romero-Salinas, G., Yoshida, T., Poseiro, J. J., and Caldeyro-Barcia, R.: Aortocaval compression by the uterus in late human pregnancy. II. An arteriographic study, Ам. J. OBSTET. GYNECOL. 100:203, 1968.
- 12. Coutts, W. E., Opazo, L., Bianchi, T. B., and Donoso, O. S.: Abdominal circulation during late pregnancy as shown in aortograms, Am. J. Obstet. Gynecol. 29:566,
- 13. Leriche, R., and Morel, A.: The syndrome of thrombotic obliteration of the aortic bifurcation, Ann. Surg. 127:193,
- 14. Abitbol, M. M., Gallo, G. R., Pirani, C. L., and Ober, W. B.: Production of experimental toxemia in the pregnant rabbit, Am. J. OBSTET. GYNECOL. 124:460, 1976.

#### Copyright information

The appearance of a code at the bottom of the first page of an original article in this JOURNAL indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc., 21 Congress St., Salem, Mass. 01970, (617)744-3350, for copying beyond that permitted by Section 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale. For reprint quantities of 50 or more, please contact Publisher.

## Maternofetal electrical potential difference in conscious sheep: Effect of fetal death or acidosis

A. P. WEEDON\*

T. E. STACEY\*\*

JANE F. CANNING

R. H. T. WARD

R. D. H. BOYD

London, England

Maternofetal electrical potential difference (pd) was measured in conscious pregnant ewes during the last 40 days of gestation. Recordings were made via catheters filled with saline solution and chronically implanted in at least two blood vessels on either side of the placenta. The pd ranged between -14 and 93 mV, mother positive. The mean potential declined from  $54 \pm 8$  mV (n = 5) immediately after operation to  $28 \pm 7$  mV after 48 hours and did not alter significantly thereafter. The pd increased with fetal acidosis induced by infusion of acid. The mean slope was  $54 \pm 11$  mV per pH unit (n = eight infusions). The pd rose when the fetus died, but was abolished by killing the ewe. The pd 1 day postoperatively fell with increasing gestational age (pd =  $164 - 1.00 \times days$ ; p < 0.05, n = 41 sheep). (Am. J. Obstet. Gynecol. 138:422,1980.)

A MATERNOFETAL electrical potential difference (pd), mother positive, has been reported for the anesthetized goat, <sup>1, 2</sup> sheep, <sup>2</sup> guinea pig, <sup>3</sup> and preterm human fetus, <sup>4</sup> and, mother negative, for the rat. <sup>3, 5</sup> Human fetuses at term <sup>6</sup> and rabbits <sup>3</sup> are reported to show a zero pd. We describe in this article the pd that can be measured in conscious sheep and its relation to fetal death and acidosis. <sup>7</sup>

#### Methods

**Surgical procedures.** Pregnant sheep in the last 40 days of gestation were catheterized under anesthesia

From the Departments of Paediatrics and Obstetrics, University College Hospital Medical School, The Rayne

Financial support was provided by The Wellcome Trust, The Birth Defects Fund, and the Queensland Children's Research Foundation.

Received for publication March 17, 1980.

Accepted June 18, 1980.

Reprint requests: Dr. R. D. H. Boyd, Department of Paediatrics, University College Hospital Medical School, Rayne Institute, 5 University Street, London, WC1E 6JF, England.

\*Present address: Royal Women's Hospital, Brisbane, Australia.

\*\*Present address: Clinical Research Centre, Northwick Park Hospital, Watford Road, Harrow, Middx. HAI 3UJ, England. and aseptic conditions as previously described.<sup>8</sup> Vinyl or silicone rubber catheters up to 1.5 mm outer diameter were inserted into at least two maternal blood vessels (femoral artery, femoral vein, uterine vein, and jugular vein) and at least two fetal vessels (hind-limb artery, hind-limb vein, umbilical vein). In five sheep (seven conceptuses), catheters of similar size or ones of larger bore (3 mm outer diameter) were also placed in the amniotic sac. In three sheep (five conceptuses) a single catheter was placed in the allantoic sac. Catheters were brought out through the flank of the ewe and kept filled with heparinized saline solution (100 to 500 units/ml) between experiments. The day of operation was defined as day 1.

Potential difference measurements. The experimental technique is illustrated diagrammatically in Fig. 1. The free ends of each of a pair of catheters were connected via sterile three-way taps (Vygon) and extension tubing (Portex disposable manometer line 200/490/200) filled with 150 mM saline solution to matched calomel half-cells (EIL Electronic Limited); these, in turn, were connected to a voltmeter of high impedance (approximately 10<sup>15</sup> ohm, Vibron Electrometer, model 33B). The pd could be monitored on the voltmeter, and a continuous tracing was obtained on a chart recorder. The recording apparatus was calibrated on each occasion by means of a Precision Millivolt Source (Comark Ltd., No. 2301). In all results

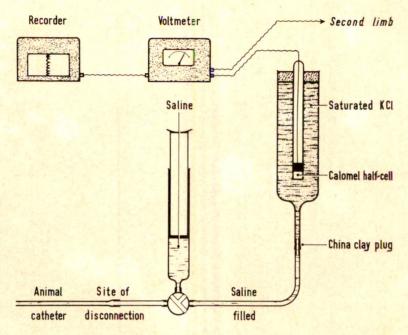


Fig. 1. Diagram showing voltmeter and one limb of circuit. Second limb, which is identical, would be connected to another chronically implanted catheter in mother, fetus, amnion, or allantois before recording pd. Saline-filled syringe is used to flush through catheter to ensure a bubble-free circuit.

quoted for a maternal catheter relative to another catheter, the nonmaternal catheter is defined as zero. In measurements recorded between a fetal catheter and amniotic or allantoic catheter, the sac catheter is taken as zero. The word increase is used to denote an increase in the numerical value of the pd recorded.

During each set of measurements, the attachment of the animal catheters to the extension tubing was reversed in order to allow for correction of any asymmetry between the calomel half-cells. Measurements were usually also made of pd recorded between different catheters within the same maternal vascular or fetal vascular "compartment" and were normally close to zero (Fig. 2, D). Readings were discarded if the "within compartment" pd was more than 7 mV, as was the case in only 2.5% of the first 120 records. Adequate placement of amniotic catheters was less easy. This difficulty was reflected in more frequent amniotic-amniotic within-compartment pd records over 7 mV. Fifteen percent of amniotic records were discarded for this reason. Only single catheters were placed in the allantoic sac, so that within-compartment checks were not made.

Checks on methodology. Although the electrical resistance of the saline solution-filled catheters and calomel half-cells was high (approximately  $6 \times 10^6$ ohms when compared in a circuit with known resistances), the internal resistance of the electrometer was several orders of magnitude higher, thus minimizing potential drop along the catheters.

Certain potential artifacts were investigated, on at east one occasion, in preliminary experiments in which the recording arrangements were altered. (1) Errors induced by variable resistance in the extra-animal circuit: recording was made through catheters with a twofold range of radii or after the addition of 400 cm of saline solution-filled tubing to one limb of the circuit. (2) Potentials induced by blood flow or blood vessel walls: the maternal vascular catheter was replaced with a subcutaneous potassium chloride agar catheter, in neither case was a potential change of more than 5 mV recorded. (3) Diffusion potentials at the catheter to blood or body fluid interface: recordings of junctional potential in vitro between saline solution and maternal, or fetal, blood or amniotic fluid were much less than 5 mV.

Wildly erratic and unstable readings were obtained if bubbles were not flushed out of the catheters or connections, presumably as a result of a vastly increased resistance and consequent large drop in potential along the measuring circuit. This may also have been the explanation for the rarely found within-compartment pd mentioned earlier. In these, an electrical connection may have been attenuated, perhaps by bubble or clot, or both. Screening of the animal cart with wire mesh, connected to earth, was found to reduce the amount of

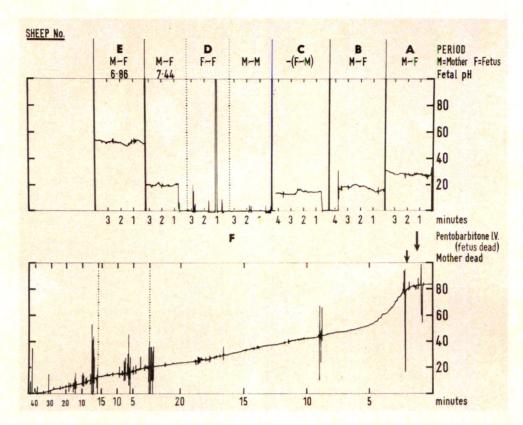


Fig. 2. Recording of pd on a number of occasions from one pregnant sheep (76-9). Sudden deviations on trace are from observer or sheep movement artifact. Ordinate: pd (mV); abscissa: time (right to left). Upper panel: A, Day 2. Maternal artery to fetal artery pd = 28 mV, mother positive (sodium flux experiment performed<sup>9</sup>). B, Day 3. Maternal artery to fetal artery pd = 17 mV, mother positive. C, Day 3. Fetal artery to maternal artery (polarity of recorder reversed) pd = 15 mV, mother positive. D, Day 5. Maternal artery to maternal vein pd = -1 mV; fetal artery to fetal vein pd = -1 mV; maternal artery to fetal artery pd = 20 mV, mother positive. Fetal arterial pH during recording = 7.44. E, Later on day 5. Fetus acidotic following spontaneous deterioration; maternal artery to fetal artery pd = 53 mV, mother positive. Fetal arterial pH = 6.86. Lower panel: Later on day 5. Fetus dead. Initially maternal artery to fetal artery pd = 84 mV; mother then killed with intravenous pentobarbitone. pd declined asymptotically to zero, and time for reduction to half initial pd = 9 minutes. (Tracing slowed twice toward end of decline.)

electrical noise induced by movement of bystanders.

Other measurements. Arterial pH was measured on heparinized samples with a Radiometer pH electrode. Plasma sodium was measured on a Technicon Autoanalyzer Mark II.

Alteration of fetal pH. In eight experiments, fetal pH was altered by intravascular infusion of acid or alkali to the fetus. The amount needed in each experiment was titrated by frequent measurement of fetal arterial pH. Maternal arterial pH was also recorded. The acids used were hydrochloric or lactic, and the amount necessary ranged from 4 to 96 mEq. The alkali used was either sodium hydroxide or sodium bicarbonate, and the amount necessary ranged from 8 to 90 mEq. In seven further experiments the carbonic

anhydrase inhibitor acetazolamide (approximately 50 mg/kg estimated fetal weight) was given intravenously to the fetus before infusion of acid or alkali. The most easily controllable method of changing fetal pH appeared to be with acetazolamide followed by an infusion of hydrochloric acid (200 mEq/liter) or sodium hydroxide (200 mEq/liter) at a rate of 0.25 mEq/minute.

Induced flows of water across placenta. In three sheep, 500 ml of 25% mannitol was injected into the maternal circulation in order to induce a transplacental flow of water. The pd was recorded before and after, and in one case during, the injection. The degree of transplacental dehydration was estimated from changes in fetal plasma sodium concentration.

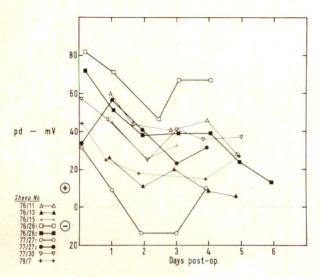


Fig. 3. Daily variation in maternofetal pd in seven pregnant sheep (nine fetuses).

Maternal death. In six experiments, the mother was killed with intravenous pentobarbitone during recording of the maternofetal pd.

Catheter positions. The positions of the catheters were confirmed by sampling or by subsequent postmortem examination.

#### Results

Resting maternofetal potential differences. The pd between mother and fetus was recorded prior to any attempts to induce changes in fetal pH on 82 days in 42 sheep. The timing of the recording sessions varied from the immediate postoperative period to 8 days postoperatively. A wide range of pds was recorded (mother - 14 with reference to fetus to +93 with reference to fetus). The mother was positive to the fetus on all but three occasions. The tracing appeared steady from minute to minute, apart from momentary deviations induced by observer or animal movement (Fig. 2). Over periods of several minutes the tracing usually showed fluctuation over a range of approximately 10 mV, but there was considerable variation in the pattern. Over a longer period the fluctuations were greater; thus, in one animal with a continual tracing for 27 of 31 consecutive hours the pd varied within the range +49 to +93 mV.

Time after surgical procedures. In seven sheep (nine fetuses), repeated recordings were made daily up to 6 days postoperatively (Fig. 3). The variation from day to day and the different values recorded from twin fetuses are apparent. Of interest is the observation that on 2 days the maternofetal pd for twin fetuses in the same mother were of opposite polarity.

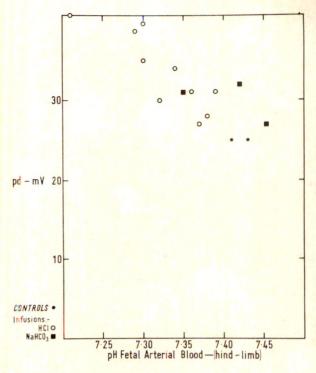


Fig. 4. Sheep 79-l. pd recorded between catheters in maternal femoral vein and fetal pedal artery 1 day after operation. Readings during control period are indicated by . Readings during infusion of 68 ml of N/10 and then 55 ml of N/5 hydrochloride acid intravenously to the fetus over 3 hours are indicated by o. Recordings during subsequent fetal infusion of 28 ml of M sodium bicarbonate over 30 minutes are indicated by .

The pd at the end of the operation gave the highest value,  $54 \pm 8$  mV mother positive (n = five lambs). The pd measured after 48 hours,  $28 \pm 7$  (n = nine lambs), was always less than that measured after 24 hours,  $43 \pm 7$  (n = nine lambs) (paired t test p < 0.002), but pd did not alter subsequently during the week after the operation (pd days 4 to  $6 = 30 \pm 7$ , n = nine lambs, 21 observations).

Fetal pH. In eight experiments in seven animals, the fetal pH was deliberately changed by more than 0.15 pH units while the maternofetal pd was being recorded (Fig. 4; Table I). In six of these experiments there was a significant inverse correlation between pd and maternofetal pH. The mean slope of pd against fetal arterial pH was  $54 \pm 11$  mV/pH unit. It is noteworthy that the slope was not uniform even on different days in the same animal (e.g., animal 76-18 in Table I). The pd extrapolated to, or measured at, zero maternofetal arterial pH difference was always positive. In one experiment, alkali was infused before acid and there was a significant inverse correlation between rising fetal pH and falling pd (p < 0.001).

Table 1	. Parameters of linear	regression:	Maternofetal	pd	on fetal	arterial	На	during	infusion a	of acid	or alkal	:

Sheep (day after operation)*	Slope	Intercept at pH = 0	No. of measurements	P	pH range	Acid/alkali infused to fetus	pd at zero maternofetal pH difference
75-28							1 33
(1) 76-18	-81	620	8	< 0.001	7.16-7.34	NaOH/NaHCO <sub>3</sub>	24†
(3) (5) 76-19	-5 -87	69 663	15 27	NS <0.001	7.26-7.44 7.15-7.42	HCl/NaHCO <sub>3</sub> Lactate/NaHCO <sub>3</sub>	27† 8†
(4) 78-20	-11	106	11	NS	7.00-7.40	Lactate/NaHCO <sub>3</sub>	32
(2) 79-1	-80	610	19	< 0.001	7.11-7.37	HCl/NaOH/NaHCO <sub>3</sub>	2
(2) 79-2	-63	494	15	< 0.001	7.21-7.45	HCl/NaHCO <sub>3</sub>	24
(2) 79-7	-71	557	17	< 0.001	7.11-7.44	HCl/NaHCO <sub>3</sub>	25
(5) Mean ± SE	$-32$ $-54 \pm 11$	$258$ $422 \pm 80$	33	< 0.001	7.27-7.47	HCl	-‡

<sup>\*1 =</sup> Day of operation.

In all seven experiments in which the fetus was treated with acetazolamide before acid/alkali infusions, there was a significant regression of pd on fetal pH. The mean slope and intercept of the regression lines were insignificantly different from the mean values for animals treated with acid and alkali alone.

**Fetal death.** Fetal deterioration or death always resulted in an increase in maternofetal pd. In six animals in which a recording was available within 24 hours before and after fetal death, there was a rise in pd of  $35 \pm 7$  mV (paired t test p < 0.01).

**Maternal death.** In five preparations, after fetal death had occurred, the mother was killed with a large dose of pentobarbitone while the maternofetal pd was being recorded. The pd tracing fell to zero after the cessation of respiration. The time taken to fall to half the initial value was  $7.8 \pm 1.5$  minutes (e.g., Fig. 2).

Potential difference and gestational age. In 41 animals of known gestational age a control measurement of pd was made on day 2 before the use of any drugs or infusions of acid. In all but six a simultaneous fetal hind-limb arterial pH was also available. The pd recorded fell with increasing gestation (range, 117 to 143 days).

pd = 
$$164 - 1.00 \times (days of gestational age)$$
  
(n = 41 sheep, r = 0.34, p < 0.05)

There was not a significant regression on pH or, in a multiple regression analysis, on pH and gestational age taken together when each animal studied on day 2 was taken as a single point. The range of pH values in these measurements was 7.24 to 7.47.

Effect of induced transplacental water flow. After injection of 125 gm of mannitol to the mother, the fetal plasma sodium concentration rose by between 7 and 20 mEq/liter, a rise which could have been effected by transplacental water flows in the range of 2.5 to 5 ml/minute for an extracellular fluid compartment two thirds of fetal weight. The pd recorded after mannitol was in each case slightly, but significantly, above the control value (range of mean rise, 5 to 9 mV; three sheep). However, in the only sheep in which a pd record without interference was achieved during the injection of mannitol, the pd did not change during the period of maximum water flow. Furthermore, the rise in pd after the injection of mannitol was in each case associated with a drop in fetal pH.

Amniotic and allantoic potentials. The pd between mother and amnion was measured in 21 recording sessions in five sheep (11 fetuses). Mother-amniotic pd were  $45 \pm 3$  (n = 21 observations). Mother-fetus pd was  $33 \pm 5$  (n = 21). The mother was always positive to the amniotic sac, even on two occasions when the mother was negative to the fetus. The maternoamniotic pd exceeded the maternofetal pd by  $13 \pm 2$  mV, and, as expected for measurements between any two of three points in a circuit, the directly measured fetus-amniotic sac pd was approximately the same. (Difference between measured and calculated fetus-amniotic pd was  $0 \pm 1$  mV.) The fetus was negative with regard to the amniotic sac on one occasion.

In 27 recording sessions in three sheep (five lambs) the pd between mother and allantoic sac was recorded, and the mother-allantoic pd was  $51 \pm 7$  (n = 27);

<sup>†</sup>Estimated by extrapolation to zero pH difference.

<sup>‡</sup>No maternal arterial sample.

mother-fetal pd was  $34 \pm 4$  (n = 27). On six of these occasions the mother was negative with regard to the allantoic sac, and in these the fetus was also negative with regard to the allantoic sac. The difference between the measured fetoallantoic pd and that calculated from the difference in maternoallantoic and maternofetal pd was again insignificantly different from zero  $(-1 \pm 1 \text{ mV}, n = 25)$ .

#### Comment

Effect of gestational age and time after surgery. A fall in pd with increasing gestational age was previously noted by Meschia and associates1 in goats, but not by Mellor.<sup>2</sup> It is in keeping with the zero potential in vivo in both human fetuses6 and rats3 at term, but not earlier,3,4 and with the decline in trophoblastic transmembrane potential as gestation proceeds.13

Our mean value for pd immediately after surgery (54 ± 8 mV) was close to values reported for anesthetized sheep.2 The mean pd after recovery was some 25 mV lower, but was noticed to rise again during spontaneous deterioration of the fetus, as well as during induced acidosis (Fig. 2). Presumably, a similar rise was brought about during surgery.

Nature and implications of potential difference. Two hypotheses have been put forward to explain the generation of a maternofetal pd. On the one hand, Thornburg and associates<sup>10</sup> propose a model circuit in which the electromotive force is not located in the placenta but elsewhere, namely, in the paraplacental chorioallantoic membrane. The basis of their model is the observation that the steady-state ratios (between maternal and fetal plasma) for bromide, lithium, perhaps sulfate, and, in the guinea pig,11 rubidium are close to one, whereas, at equilibrium, two solutions separated by an inert permeable barrier across which there is a substantial drop in voltage should have grossly asymmetric distributions of ions. In their circuit they split the electrical resistance into a transplacental component estimated at 0.06 ohm from placental conductivity toward radiolabeled sodium chloride (this gives a resistance of some 6,000 ohms · cm<sup>-2</sup>, a reasonable value for a tight epithelium), and a further resistance of 0.27 ohm proposed to exist between the placental capillaries and the large blood vessels from which pd measurements have been recorded. Our observation that maternofetal pd is trivially different, regardless of the arterial or venous site of recording electrode, is incompatible with this model, unless it is further assumed that an identical electrical resistance is present both between placental capillary and peripheral artery via the arteriolar circulation of the placenta, and between placental capillary and peripheral vein via the venular end of the placental capillary. This seems to be very unlikely.

An alternative model, which we at present prefer, is one in which there is an important transplacental pd together with an array of transplacental ion pumps. The latter are themselves probably electrogenic and thus provide the electromotive force for the circuit. Evidence to support the idea of a specifically transplacental pd includes the observations that a potential can be recorded across the perfused guinea pig placenta in the absence of a fetus, 12 that trophoblast membrane microvesicles accumulate amino acids in an ion-dependent manner,14 and that the maternofetal potassium concentration ratio in the rat is equal to that predicted for equilibrium from the observed electrochemical gradient.5 It should also be noted that in an organ in which pd recorded at a distance through vascular catheters can be compared with transepithelial pd measured in vitro, namely, the gut, the two methods give similar results. Thus, colonic transepithelial pd is about the same whether measured in vivo between a luminal and an extraluminal electrode, be the latter in submucosa or in the jugular vein,15 or in vitro with the use of an intestinal epithelial layer stripped free of overlying muscle and mounted in a chamber.16

Generation of a pd at the placental exchange area could occur through one of three mechanism. The first possibility is a streaming potential, but this is unlikely because of the small change in pd noticed after the induction of even quite unphysiologic flow rates. A diffusion potential of potassium17 or hydrogen ion is a second possibility. The former is rendered unlikely as a simple cause of the pd, because of the substantial net transport of K+ toward the fetus, which would generate the wrong polarity. The possibility that the placenta acts as a hydrogen electrode might appear attractive, in view of the net production of acid by the fetus, together with our demonstration of a rise in pd dependent on fetal pH, analogous to the rise in cerebrospinal fluidblood potential on systemic acidosis.18 However, the persistence of a pd at zero maternofetal pH difference rules out a simple transplacental H+ diffusion potential as the mechanism. Nevertheless, fetal pH obviously influences pd profoundly in the short term but not, as the absence of relationship between resting pH and pd demonstrates, in the long term.

We support the third possibility of transplacental electrogenic ion pumps. Stulc and Svihovek12 first suggested, on the basis of an observed diminution in the pd when the placenta is perfused with sodium-free media, that the pd is partly generated by a maternally directed sodium pump, and bidirectional sodium flux measurements in the sheep support this idea.9 A maternally directed pump for sodium only becomes biologically possible, however, if a fetally directed negative ion pump is also active. It must be confessed that direct evidence for such a pump is not at present available.

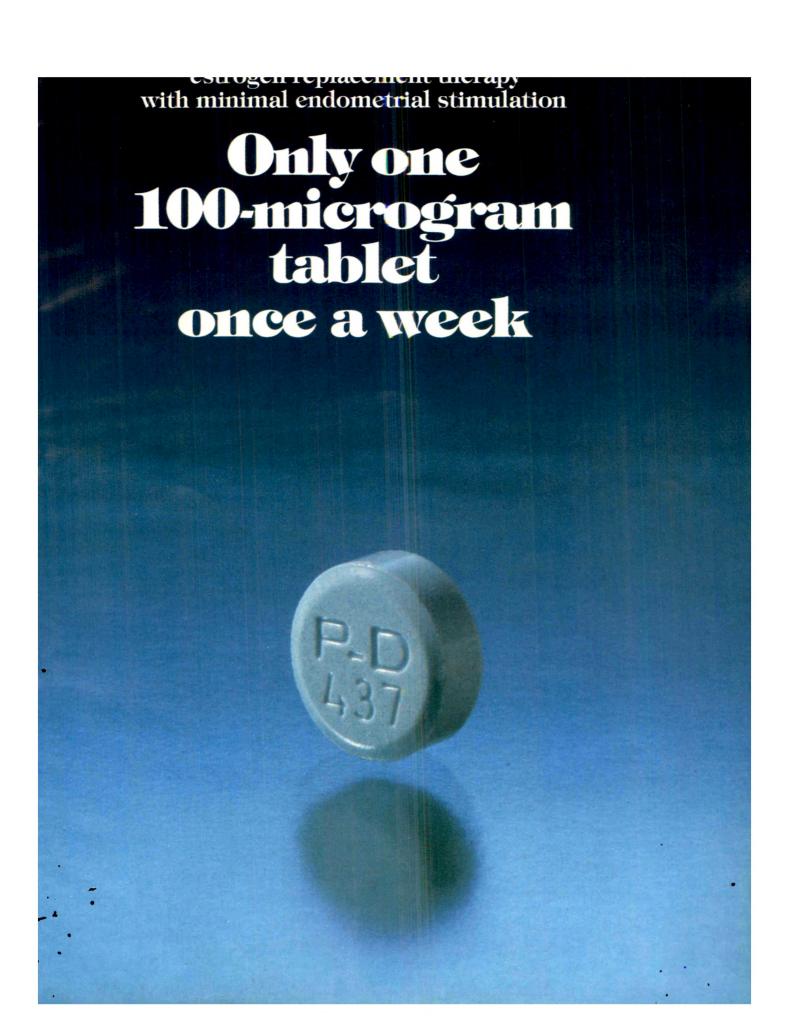
The dependence of the pd on the pH demands that either pump activity or transplacental resistance is influenced by changing pH. The rise in pd after fetal death is also unexplained and could occur because of an increase in transplacental resistance (unlikely), overactivity of an ion pump normally controlled by the fetus, or a diffusion of ions across the placenta induced by the unsteady state associated with fetal dissolution.

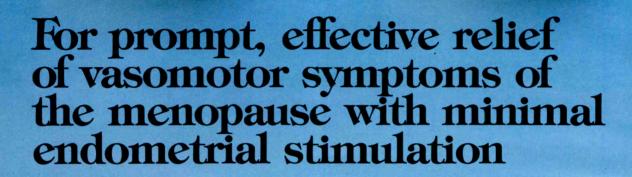
We wish to thank Mr. Michael Bright and Mr. Steven Brown for invaluable technical assistance. Discussion with Dr. C. J. Edmonds was most helpful.

#### REFERENCES

- Meschia, G., Wolkoff, A. S., and Baron, D. H.: Difference in electrical potential across the placenta of goats, Proc. Natl. Acad. Sci. U.S.A. 44:483, 1958.
- Mellor, D. J.: Distribution of ions and electrical potential differences between mother and fetus at different gestational ages in goats and sheep, J. Physiol. 207:133, 1970.
- 3. Mellor, D. J.: Potential differences between mother and fetus at different gestational ages in the rat, rabbit and guinea pig, J. Physiol. **204**:395, 1969.
- Stulc, J., Svihovek, J., Dravkova, J., Stribrny, J., Kobil-kova, J., Vido, I., and Dolezal, A.: Electrical potential difference across the mid-term human placenta, Acta Obstet. Gynecol. Scand. 57:125, 1978.
- Fantel, A. G.: Fetomaternal potassium relations in the fetal rat on the twentieth day of gestation, Pediatr. Res. 9:527, 1975.
- Mellor, D. J., Cockburn, F., Lees, M. M., and Blagden, A.: Distribution of ions and electrical pd between mother and fetus in the human at term, J. Obstet. Gynaecol. Br. Commonw. 76:993, 1969.
- Weedon, A. P., Stacey, T. E., Boyd, R. D. H., and Ward, R. H. T.: Feto-maternal electrical potential in the conscious sheep, Pediatr. Res. 10:891, 1976.
- Boyd, R. D. H., Haworth, C., Stacey, T. E., and Ward, R. H. T.: Permeability of the sheep placenta to unmetabolized polar non-electrolytes, J. Physiol. 256:617, 1976.
   Weedon, A. P., Stacey, T. E., Ward, R. H. T., and Boyd,
- Weedon, A. P., Stacey, T. E., Ward, R. H. T., and Boyd, R. D. H.: Bidirectional sodium fluxes across the placenta of conscious sheep, Am. J. Physiol. 235:F536, 1978.

- Thorburg, K. L., Binder, N. D., Faber, J. J.: Distribution of ionic sulphate, lithium and bromide across the sheep placenta, Am. J. Physiol. 236:C58, 1979.
- 11. Binder, N. D., Faber, J. J., and Thorburg, K. L.: The transplacental potential difference as distinguished from the maternal-fetal potential difference of the guinea pig, J. Physiol. **282**:561, 1978.
- 12. Stule, J., and Svihovek, J.: Effects of potassium cyanide, strophanthin or sodium-free perfusion fluid on the electrical potential difference across the guinea pig placenta perfused in situ, J. Physiol. **231**:403, 1973.
- Cartstensen, M., Leichtweiss, H. P., and Schröder, H.: Zellpotentiale in der Placenta des Menschen, Arch. Gynecol. 215:299, 1973.
- Bóyd, C. A. R., and Lund, E. K.: Neutral amino acid transport into micorvillus membrane vesicles prepared from human placentae. J. Physiol. 291:29P, 1979.
- 15. Edmonds, C. J.: The gradient of electrical potential difference and of sodium and potassium of the gut contents along the caecum and colon of normal and sodium-depleted rats, J. Physiol. 193:571, 1967.
- Edmonds, C. J., and Marriot, J.: Electrical potential and short circuit current of an in vitro preparation of rat colon mucosa, J. Physiol. 194:479, 1968.
- 17. Stulc, J. J., Rietveld, W. J., Soeteman, D. W., and Versprille, A.: The transplacental potential difference in guinea-pigs, Biol. Neonate 21:130, 1972.
- Held, D., Fencl, V., and Pappenheimer, J. F.: Electrical potential of cerebrospinal fluid, J. Neurophysiol. 27:942, 1964.





# ESTROVIS® (quinestrol)

### Low maintenance dosage regimen of Estrovis

one 100-microgram tablet <u>once</u> <u>a</u> <u>week</u> (beginning two weeks after starting priming regimen of one tablet <u>daily</u> for seven days)

Cut out and mail to:

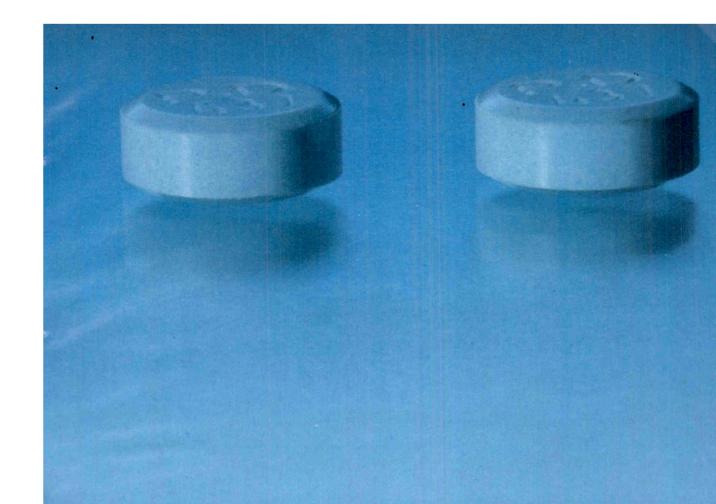
	Lambert Co NJ 07950 USA	Offer Expires 6/30/81
Attn: B. Howa Please send no Estrovis® (qu	ne a free supply of Patie	ent Trial Packs of
Printed Name of Signature of Physics		
Street Address		
City	State	Zip

## Minimal endometrial stimulation at recommended dosage

Studies suggest a wide separation between symptomatic therapeutic effects and endometrial stimulation.

## Efficacy and tolerance of Estrovis®(quinestrol) well established

The therapeutic effectiveness, tolerance, and safety of Estrovis have been studied in more than 1700 women. Total experience comparing Estrovis to other synthetic estrogens and conjugated estrogens demonstrated a prompt, smooth onset of action; a characteristic pattern of smooth, downward regression of flushes over time... no ups and downs of relief; excellent tolerance over lengthy periods of treatment.



#### A distinct metabolic profile

in vivo studies indicate Estrovis® (quinestrol) is

- Rapidly absorbed
- Stored in fatty tissue as unchanged quinestrol (Estrovis)
- Slowly metabolized to active estrogen, ethinyl estradiol

## Effective clinical results shown in a recent multicenter study†

Therapeutic results of double-blind controlled tudy of 156 patients comparing Estrovis to onjugated estrogens and placebo confirmed once—week Estrovis regimen as effective as a daily egimen of conjugated estrogens (cyclic basis); ommon estrogenic side effects with Estrovis omparable to those with conjugated estrogens; elief of flushes obtained more rapidly with 'strovis—during first week's priming regimen batient evaluation).

aumgardner SB, Condrea H, Daane TA, et al: Replacement estrogen terapy for menopausal vasomotor flushes. Obstet Gynecol 51: 445, 978.

## Simple, convenient dosage schedule

Priming regimen: one 100-microgram tablet daily for seven days.

Maintenance regimen: one 100 microgram tablet weekly the reafter beginning two weeks after starting therapy.

				and the last of th	- Indianal and	The Later		
	1st week	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	2nd week			TAKE	NO TA 	BLETS 		
1	3rd week	Day 1						
	4th week	Day 1						
	5th week	Day 1						

Please see brief summary of prescribing information on following page.

### **ESTROVIS**°

(quinestrol)

The proper dosage of the proper estrogen for the proper patient

**PARKE-DAVIS** 

### **ESTROVIS**® (quinestrol)

#### The proper dosage of the proper estrogen for the proper patient

scribing Information including references and patient insert are available on request.) CAUTION
Federal law prohibits dispensing without prescription.

WARNING

1. Strogens Have Been Reported to Increase the Risk of Endometrial Carcinoma.

Three independent case control studies have shown an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for prolonged periods. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1959 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.

The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms the lowest dose that will control symptoms should be undertaked, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration, it, therefore, appears prudent to utilize such a regimen.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy.

There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic"

malignancy.
There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. Estrogens Should not be Used During Pregnancy.
The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrot, a monsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenoiss, epithelial changes of the vagina and cervix. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies; including congenital heart defects and limb-reduction defects. One case control study estimated a 4.7 fold increased risk of limb-reduction defects in infants exposed in utero to sex hormones coral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion. Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat tests than 1 per 1000.

In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these uses.

If Estrovis (quinestrol) is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

UCSCKIP'IIUN

Estrovis (quinestrol) is available as a 100 mcg oral tablet. It is an estrogen.

Estrovis (quinestrol) is the 3-cyclopentylether of ethinyl estradiol. The chemical name is 3-cyclopentyloxy-17α-ethynylestra-1,3,5(10)-trien-17β-οl.

It is a white, essentially odorless powder, insoluble in water and soluble in alcohol, chloroform, and ether.

CLINICAL PHARNACOLOGY

ELIMICAL PHARMACULOEY
Estrovis (quinestrol) is an orally effective estrogen as judged by conventional assay procedures employing vagina and uterine end-points in mice, rats and rabbits.
The estrogenic effects of Estrovis have been demonstrated in clinical studies by its effects on the endometrium, maturation of the vaginal epithelium, thinning of cervical mucus, suppression of pituitary gonadotropin, inhibition of ovulation, and prevention of postpartum breast discomfort.

INDICATIONS

Estrovis (quinestrol) is indicated in the treatment of: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions.) 2. Atrophic vaginitis 3. Kraurosis vulvae 4. Female hypogonadism 5. Female castration 6. Primary ovarian failure

Estrovis (Quinestrol) Has Not Been Shown to be Effective for any Purpose during Pregnancy and Its Use May Cause Severe Harm to the Fetus (See Boxed Warning).

CONTRAINDICATIONS

Estrogens should not be used in women (or men) with any of the following conditions.

1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.

2. Known or suspected estrogen-dependent neoplasia 3. Known or suspected pregnancy ese Boxed Warning)

4. Undiagnosed abnormal genital bleeding 5. Active thromopoelhebits or thromboembolic disorders 6. A past history of thrombophlebits, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in

WARNINGS

I. Induction of malignant neoplasms. Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There is now evidence that estrogens increase the risk of carcinoma of the endometrium in Inhumans. (See Boed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent long-term followup of a single physician's practice has raised this possibility. Because of the animal data, there is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms.

2. Gallbladder disease. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallblad disease in women receiving postmenopausal estrogens, similar to the 2-fold increase previously noted in users of a contraceptives. In the case of oral contraceptives in the case of oral contraceptives. There are several serious adverse effects oral contraceptives, most of which have not, up to now, been documented as consequences of postmenopausal estro herapy. This may reflect the comparatively low doses of estrogen used in postmenopausal women. It would be expect that the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement are more life to result in these adverse effects, and, in fact, it has been shown that there is an increased risk of thrombosis in a receiving estrogen for prostatic cancer and women for postpartum breast engorgement.

a. Thromboembolic disease. It is now well established that users of oral contraceptives have an increased risk of a prost intromboembolic and thrombotic vascular diseases, such as thrombophelbits, pulmonary embolism, stroke, and myocar infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptives. If feasil estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk thromboembolism, or during periods of prolinged immobilization.

While an increased rate of thromboembolic and thrombotic disease in postmenopausal users of estrogens has not bround, this does not rule out the possibility that such an increase may be present or that subgroups of women who inunderlying risk factors or wha are receiving restored by the prost of the disorders in association with estrepone, strongers are clearly needed.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate a breast, have been shown in a large prospective clinical trial in men to increase the ris

reported in women taking estrogen-containing oral contraceptives. The relationship of this malignancy to these drugs is known at this time.

c. Elevated blood pressure. Increased blood pressure is not uncommon in women using oral contraceptives. There is no report that this may occur with use of estrogens in the menopause and blood pressure should be monitored with estroguse, especially if high doses are used.

d. Glucose tolerance. A worsening of glucose tolerance has been observed in a significant percentage of patients estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while received to the contraceptives.

dugen.

Hypercalcemia. Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and be tastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium ler

metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium les 
PRECAUTIONS

A. General Precautions

1. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatm and periodic physical examinations should include special reference to blood pressure, abdomen, and pelvic organs, a should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year with another physical examination being performed.

2. Fluid retention—Because estrogens may cause some degree of fluid retention, conditions which might be influenced this factor, such as epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

3. Certain patients may develop undesirable manifestations or excessive estrogenic stimulation, such as abnormal excessive uterine bleeding, mastodynia, etc.

4. Oral contraceptives appear to be associated with an increased incidence of mental depression. Although it is not climbether this is due to the estrogenic or progestogenic component of the contraceptive, patients with a history of depress should be carefully observed.

whether this is due to the estrogenic or progestogenic component of the contraceptive, patients with a history of depress should be carefully observed.

5. Preexisting uterine leiomyomata may increase in size during estrogen use.

6. The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

7. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice where receiving estrogen-containing oral contraceptive therapy. If jaundice develops in any patient receiving estrogen, medication should be discontinued while the cause is investigated.

8. Estrogens may be poorly metabolized in patients with impaired liver function and they should be administered we caution in such patients.

9. Because extragens influence the metabolizm of calcium and phosphorus, they should be used with caution in patie.

o. causion in such patients.

9. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patier with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

10. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whome growth is not complete.

11. Certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The followis similar changes may be expected with larger doses of estrogen: a. Increased sulfobromophithalein retention. b. Increase prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3; increased norepinephrine-induced platelet a gregability. C. Increased through binding globulin (TBG) leading to increased circulating total thyroid hormone, as measus by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free concentration is unaltered. d. Impaired glucose tolerance. e. Decreased pregnanediol excretion. f. Reduced response metryapone test, g. Reduced serum folate concentration. h. Increased serum friglyceride and phospholipid concentration. B. Increased serum friglyceride and phospholipid concentration. B. Increased serum folate concentration. B. Increased serum friglyceride and phospholipid concentration. B. Increased serum folate concentration. B. Increased serum folate concentration. B. On Winsing Mothers. As a general principle, the administration of any drug to nursing mothers should be done only wt clearly necessary since many drugs are excreted in human milk.

AVMERSE REACTIONS

(See Wannings regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disea

ADVERSE REACTIONS

(See Warnings regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disea and adverse effects similar to those of oral contraceptives, including thromboembolism.) The following additional adverse effects similar to those of oral contraceptives, including thromboembolism.) The following additional adverage free the proported with estrogenic therapy, including oral contraceptives.

1. Genitourinary system: Breakthrough bleeding, spotting, change in menstrual flow, Dysmenorrhea, Premenstrual-syndrome, Amenorrhea during and after treatment, Increase in size of uterine fibromyomata, Vaginal candidiasis, Char in cervical eversion and in degree of cervical secretion, Cystitis-like syndrome. 2. Breasts: Tenderness, enlargeme secretion, 3. Gastrointestinal: Nausea, vomiting, Abdominal cramps, bloating, Cholestatic jaundice, 4. Skin: Chloasma melasma which may persist when drug is discontinued, Erythema multiforme, Erythema nodosum, Hemorrhagic eruptil Loss of scalp hair, Hirsutism, 5. Eyes: Steepening of corneal curvature, Intolerance to contact lenses, 6. CNS: Headact ingraine, dizziness, Mental depression, Chorae, 7. Miscellaneous: Increase or decrease in weight, Reduced carbohydriolerance. Aggravation of porphyria, Edema, Changes in libido.

ACUTE OVERDOSAGE

Numerous reports of ingestion of large doses of estrogen-containing oral contracentives by young children indicate the

umerous reports of ingestion of large doses of estrogen-containing oral contraceptives by young children indicate t rious ill effects do not occur. Overdosage of estrogen may cause nausea, and withdrawal bleeding may occur in femal

DUSAGE AND ADMINISTRATION

For treatment of moderate to severe vasomotor symptoms associated with the menopause, and for atrophic vaginit
kraurosis vulvae, female hypogonadism, female castration and primary ovarian failure.

One Estrovis (quinestrol) 100-mog tablet once daily for seven days, followed by one 100-mog weekly as a maintenar
schedule, commencing two weeks after inception of treatment. The dosage may be increased to 200 mcg weekly if t
therapeutic response is not that which may be desirable or considered optimal.

The lowest maintenance dose that will control symptoms should be chosen and medication should be discontinued
promptly as possible.

The lowest maintenance dose that will control symptoms should be chosen and medication should be discontinued promptly as possible.

Attempts to discontinue or taper medication should be made at three to six month intervals.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropria diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vagin

Dieconia, New SUPPLIED N 0071-0437 (P.D. 437) Estrovis (quinestrol) 100 microgram Tablets are supplied in bottles of 100 Tablets.

0437G020

#### **PARKE-DAVIS**

Div of Warner-Lambert Co Morris Plains, NJ 07950 USA

#### FETUS, PLACENTA, AND NEWBORN

#### Nonstressed antepartum heart rate monitoring: Implications of decelerations after spontaneous contractions

G. H. A. VISSER\*

C. W. G. REDMAN

H. J. HUISJES

A. C. TURNBULL

Oxford, England, and Groningen, The Netherlands

Fetal outcome in 98 patients with spontaneous antepartum late decelerations was studied by combining the data of two obstetric departments. Heart rate variability was used to classify the different patterns into two categories: terminal and decelerative. In 14 of the 47 pregnancies in which a terminal pattern was found, intrauterine death occurred within a week. Of the remaining 33 fetuses, 71% were acidemic at elective cesarean section (CS). In contrast, all of the 51 fetuses with a decelerative cardiotocogram (CTG) survived the antenatal period, and only two of 25 were acidemic at elective CS. Labor was induced in 20 patients with a decelerative CTG, and fetal distress occurred in 12, of whom 10 were eventually delivered by CS. All fetuses with a repetitive decelerative heart rate pattern antepartum developed distress in labor. In contrast, an isolated deceleration, on one occasion only, was not associated with distress during labor, except in growth-retarded fetuses. The clinical implications of these findings are discussed and the results are compared with those of oxytocin contraction stress tests. (AM. J. OBSTET. GYNECOL. 138:429, 1980.)

A REACTIVE or normal nonstressed antepartum cardiotocogram (CTG) is characterized by a baseline variability of more than 10 beats/minute, accelerations as a

From the Nuffield Institute for Medical Research, Oxford; the Department of Obstetrics, John Radcliffe Hospital, Oxford; and the Department of Obstetrics and Gynaecology, University Hospital, Groningen.

Received for publication March 18, 1980.

Accepted June 18, 1980.

Reprint requests: G. H. A. Visser, Department of Obstetrics and Gynaecology, University Hospital, Oostersingel 59, 9713 EZ, Groningen, The Netherlands.

\*Supported by a grant from the Royal Society, London, England. Present address: Department of Obstetrics and Gynaecology, University Hospital, Groningen, The Netherlands. reaction to fetal movements, and no decelerations. It indicates that the fetus is able to withstand labor and thus implies fetal well-being. The oxytocin challenge test (OCT) is usually normal in these cases, so that more and more investigators—if they use this test at all—restrict it to "nonreactive" patterns.

The interpretation of a positive OCT is, however, open to contradiction, and the frequency of false positive tests ranged from none among eight patients<sup>3</sup> to all among nine patients.<sup>4</sup> The reasons for this discrepancy might include the following: (1) In studies showing the highest incidence of false positive tests, remarkably high doses of oxytocin (up to 20 m $\mu$ /minute) were used.<sup>4, 5</sup> (2) Most reports contained mixed information concerning positive tests after either spontaneous or oxytocin-induced contractions (CST—contraction

**Table I.** Indications for antepartum cardiotocography and gestational age (in weeks) at delivery

		ninal TG	Decelerative CTG		
Indications	Gron- ingen	Oxford	Gron- ingen	Oxford	
Hypertensive disorders	20	6	13	13	
Eclampsia	3	_	_	_	
Suspected IUGR*	10	_	12	1	
Partial abruption	3	3	_	_	
Diabetes	_	_	-	2	
RH-sensitization	_	_	1	_	
Decreased fetal movements	1	_	4	_	
Post-term pregnancy	_	_	2	_	
Other indications	_	1	1	2	
Total	37	10	33	18	
Gestational age (in weeks) at delivery					
Mean	34.1	31.7	35.6	32	
Variation	27-38	29-38	32-41	30-38	

\*IUGR: Intrauterine growth retardation without hypertension or other pregnancy abnormalities.

stress test), the consequences of which might be different, as suggested by the findings of Gauthier and associates. (3) The interpretation of positive tests has, in general, not included allowance for heart rate variability and accelerations, which can help to discriminate between true and false positive. (4) There was a relatively small population in most of the studies. (5) The lack of adequate data at delivery (in labor CTG, micro-analyses of blood, cord pH values).

To solve part of the problem, we analyzed fetal outcome in patients with a spontaneous positive CST. By combining the data of two obstetric departments, we were able to study fetal outcome in 98 patients. Heart rate variability was used to classify the different decelerative heart rate patterns, and in most cases the cord pH was measured at delivery.

Extended data of earlier studies<sup>1, 8</sup> are included in the present study.

#### Patients and methods

Data from the Department of Obstetrics and Gynaecology of the University Hospital of Groningen, The Netherlands, were combined with data from the Department of Obstetrics of the John Radcliffe Hospital, Oxford, England.

Since 1969, all hospitalized high-risk pregnancies in Groningen have been monitored by nonstressed antepartum phonocardiotocography. In Oxford, systematic monitoring of high-risk pregnancies started in 1975. Because ultrasound was used in Oxford to monitor fetal heart rate patterns, the data will be presented separately.

The policies for heart rate monitoring in both hospitals were the same. Recordings were made with a Hewlett-Packard cardiotocograph at a paper speed of 2 cm/minute and were of at least 20 minutes' duration. Depending on the normality or abnormality of previous recordings and the presumed risk of intrauterine fetal distress, CTGs were made from once a week to two or three times a day. Recordings of longer than 20 minutes were made if the trace was of poor technical quality or if there was an abnormality. The presence or absence of uterine contractions did not influence the length of the recording, provided that the trace was "normal."

Heart rate traces showing late decelerations as a reaction to Braxton-Hicks contractions were classified according to a system developed from one in use in Groningen, first presented in 1976.9

**Decelerative CTG.** A decelerative CTG had a baseline variability of more than 5 beats/minute, at least one acceleration of more than 10 beats/minute, and late decelerations with a varying pattern not occurring after every spontaneous contraction. In an *incidental decelerative CTG*, only one deceleration was observed; and in a *repetitive decelerative CTG*, there was more than one deceleration in the same recording or on different occasions.

**Terminal CTG.** A terminal CTG had a baseline variability of less than 5 beats/minute, absence of accelerations, and repeated late, usually shallow, decelerations in relation to Braxton-Hicks contractions.

The traces of Oxford were classified retrospectively by one of the investigators (G. H. A. V.), without his having any knowledge of fetal outcome in these cases.

The data of all "terminal" CTGs, as collected in the course of the last 10 years in Groningen, will be presented, as well as the data of two studies about decelerative heart rate patterns: (1) all cases with a decelerative CTG in which labor was induced in the period from August 1, 1973, to January 1, 1976, and (2) all cases with a decelerative CTG terminated by elective cesarean section (CS) after January 1, 1976.

The Oxford data contained all patients from the high-risk clinic with a terminal CTG and decelerative heart rate pattern, delivered by elective CS since 1975.

Patients with decelerations subsequent to prolonged spontaneous contractions (>5 minutes) were excluded.

Indications for cardiotocography are presented in Table I, as is the mean gestational age at delivery.

Birth weight percentiles were calculated according to the Dutch (Kloosterman) curves<sup>10</sup> and British (Thomson) curves.<sup>11</sup>

Until 1974, in Groningen, a fetal-maternal base deficit difference (at a hemoglobin concentration of 5 gm/dl) of more than +4 was considered to indicate

1

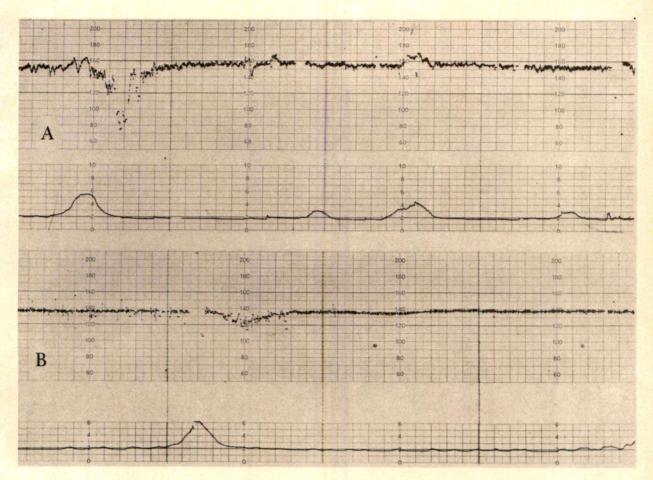


Fig. 1. Original examples of a "decelerative" (A) and "terminal" (B) cardiotocogram (paper speed, 2 cm/minute).

fetal acidemia<sup>12</sup> (N = 12). In the more recent data, acidosis at birth was defined as an umbilical artery pH of 7.15 or less.

### Results

There were 47 patients with a terminal pattern and 51 with a decelerative pattern (Fig. 1).

Intrauterine death occurred in 14 of the 47 monitored pregnancies in which a terminal pattern was found and in which it was decided, for various reasons, not to deliver the fetus. Intrauterine death occurred in all between 2 and 7 days after the first terminal pattern was recorded. Fig. 2 shows the heart rate pattern in one of these cases from 4 days before until the day of intrauterine death. The fetus died 4 hours after the last CTG shown in Fig. 2, following a "triple" contraction (Fig. 3). Bradycardia was observed only twice, in both cases just before fetal death. In the other 12 patients the heart rate was always within the normal range (120 to 160 beats/minute).

The other 33 patients with a terminal CTG were delivered by elective CS. Seventy-one percent of the infants in whom the pH was measured were acidemic at birth (Table II).

In contrast, of 25 fetuses with a decelerative CTG and cord pH measurements, only two (8%) were acidemic at elective CS (Table II).

The results from Groningen and Oxford, presented separately in Table II, are comparable with each other.

In 20 patients with a decelerative CTG—all from Groningen and previously described elsewhere1-labor was induced by amniotomy and oxytocin infusion. In all of the 10 patients who showed a "repetitive decelerative" CTG, fetal distress occurred during labor. This presented as continuing late decelerations and decreasing scalp pH; eight of the 10 patients were eventually delivered by CS. In these eight patients, more than 50% of the contractions were followed by late decelerations in the 30 minutes preceding CS. With the "incidental decelerative" CTG, fetal distress during labor occurred only when the weight of the fetus was less than that for the tenth percentile (Table III).

In the patients with a repetitive decelerative pattern,

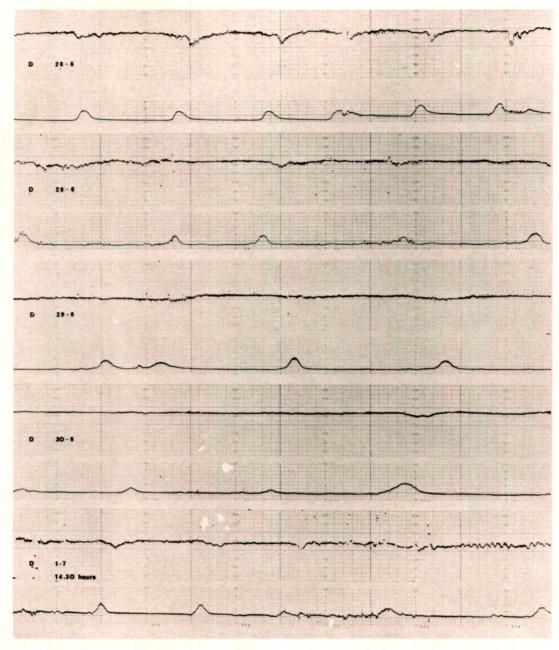


Fig. 2. Fetal heart rate pattern from 4 days before until the day of intrauterine death (paper speed, 2 cm/minute).

the mean interval between the first decelerative CTG and the time of delivery was about 5 days. In five of the 33 patients, delivery took place more than 2 weeks after the first decelerative pattern, the longest interval being 4 weeks.

Five of the 33 infants with a terminal CTG, delivered by elective CS, died neonatally, as well as 5 of the 51 infants with a decelerative CTG (Table IV). Three infants had brain damage; one case was severe, including atrophy of the optical nerve. All three infants had a

terminal heart rate pattern before birth and were acidotic at birth.

# Comment

Intrauterine death occurred within a week in all cases in which there was a spontaneous "terminal" CTG and in which the fetus was not delivered. Therefore these records can justifiably be called "terminal." The only way to prevent fetal death is immediate delivery.

Since in two thirds of the patients in whom a terminal

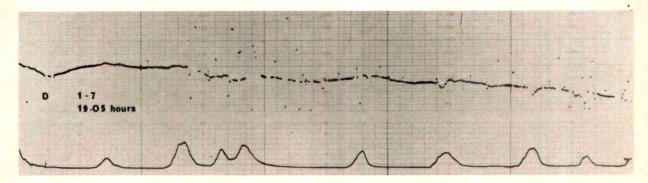


Fig. 3. "Final" bradycardia just before fetal death. Recording made 4 hours after the last cardiotocogram shown in Fig. 2 (paper speed, 2 cm/minute).

Table II. Incidence of small-for-dates (SFD; ≤tenth percentile) and acidemia (pH of umbilical artery ≤7.15) in fetuses with a terminal and decelerative CTG pattern, delivered by elective CS

			Acidemia		
Description	N	SFD	No. in which cord pH values obtained	Acidemic	
Terminal, intrauterine death					
Groningen	10	8			
Oxford	4	3			
	14	11 (79%)			
Terminal, elective CS		(,,,,,,			
Groningen	27	23	25	17	
Oxford	6	4	3	3	
	$\frac{6}{33}$	27 (82%)	$\frac{3}{28}$	20 (71%)	
Repetitive decelerative, elective CS		(/-)		== (, 1,0)	
Groningen	9	6	8	0	
Oxford	14	11	10	1	
	$\frac{14}{23}$	17 (74%)	18	1	
Incidental decelerative, elective CS	20	(/ - / / / /	.0		
Groningen	4	3	4	1	
Oxford	4	3 2 5	3	_	
	-8	5	7	1	

The fetuses with a terminal CTG who died in utero are included in this table.

heart rate pattern is recorded, the fetus is already acidemic at elective CS, pregnancy should be terminated by CS and not by induction of labor.

Except in case of a "final" bradycardia (Fig. 3), it is, in our opinion, impossible to predict exactly when a fetus with a terminal heart rate pattern will die. A "sinusoidal" heart rate pattern, observed by Kubli and associates13 in 7 of 12 dying fetuses, was found in the present study on only three occasions: 1 day and 2 days before fetal death, and 4 hours before intrauterine death (Fig. 2).

The "decelerative" CTG was characterized by a baseline heart rate variability of more than 5 beats/ minute and at least one acceleration every 20 minutes, with an amplitude of 10 beats/minute or more. This does not necessarily mean that heart rate variation and the number of accelerations in these patients was the

same as in uncomplicated pregnancies. In fact, criteria for a normal CTG include most commonly a baseline variability of 10 beats/minute or more and accelerations with an amplitude of over 15 (or even 20) beats/minute. However, these definitions do not take into account the known effect of gestational age on heart rate variation,14 and gestational age in this study was rather low (Table I). Ideally, the different abnormal patterns should be compared with each other and with heart rate patterns of normal pregnancies, by objective (computer) methods for analyzing heart rate variation.

Late decelerations, present both in the decelerative and terminal CTG, are presumably signs of fetal hypoxia.15 The present study suggests that fetal acidemia is associated with a loss of heart rate variation and accelerations. The sudden drop in fetal move-

**Table III.** Relationship between occurrence of incidental or repetitive late decelerations antepartum, birth weight percentiles, and fetal distress during labor (repetitive late decelerations, decreasing scalp pH)

CTG	Birth weight percentile	N	CS because of fetal distress	Vaginal delivery with or without fetal distress	
				With	Without
Repetitive	≤10	7	6 (3)	1*	_
decelerative	>10	3	2 (2)	1*	-
		10	8 (5)	2	
Incidental	≤10	5	2 (1)	1	2 (1)
decelerative	>10	_5	-	-	5 (1)
		10	$\frac{1}{2}$ (1)	1	7 (2)

In parentheses is shown the number of fetuses who were acidemic at birth (pH of umbilical artery ≤7.15).

\*Decreasing scalp pH below 7.20; "intrauterine resuscitation" with tocolytic agents; eventually vaginal delivery.

Table IV. Neonatal death

	Terminal CTG		Decelerative CTG	
	Gron- ingen	Oxford	Gron- ingen	Oxford
Congenital abnormality	-	1	3	_
Hyaline membrane disease	2	_	_	
Ventricular hemorrhage	1	-	-	1
Fetal death during CS*	-	-	1	_

\*Induction of labor; CS because of fetal distress, pH at delivery 6.80.

ments—which, at least in normal pregnancies, are strongly associated with heart rate accelerations—a few days before fetal death<sup>16</sup> further supports this assumption.

With the decelerative CTG, the fetus is not yet acidotic, so that there may be time to determine fetal lung maturation and, if necessary, to give steroids. If the pregnancy is very premature, it may be continued under strict cardiotocographic monitoring.

With a repetitive decelerative CTG, the fetus should be delivered by elective CS, since fetal distress occurred during labor in all patients in whom labor was induced. With the incidental decelerative CTG, fetal distress during labor was restricted to the growth-retarded infants (three of five). Because it is the very combination of growth retardation and acidemia which is associated with a high frequency of neonatal neurological morbidity,<sup>17</sup> this group should, in our opinion, be delivered by elective CS, as well.

In the appropriate-for-dates (AFD) group which showed an antepartum isolated late deceleration, no fetal distress during labor developed. Induction of labor may be justified in this group, but one can argue whether delivery is necessary at all. In this respect it is interesting to know the incidence of late decelerations in normal pregnancy. Preliminary results of 290 hours of antenatal monitoring of heart rate in 66 thirdtrimester pregnancies revealed two isolated late decelerations. In both patients, normal recordings were made afterward, and pregnancy outcome was uneventful. When antepartum monitoring of heart rate is restricted to 20 minutes, this would imply that once in ±435 recordings in normal patients a late deceleration can be found. If a late deceleration in normal pregnancy occurs by chance, the incidence of a repetitive decelerative pattern is in the order of [1/435]2. Although these are preliminary data, they might indicate that a repetitive decelerative CTG is definitely an abnormal finding and thus support the different outcome in the AFD group in this study with a repetitive decelerative CTG, in comparison with the AFD group with an isolated late deceleration.

The incidence of false positive OCTs is, according to a review which we performed in 1977, about 30% to 40%. A spontaneous terminal CTG, with an incidence of fetal acidemia of already 71% at the time of elective CS, is thus far more ominous, as is the repetitive decelerative CTG.

The present data, which stress the importance of including heart rate variation in the analysis of the positive CST, are in agreement with Braly and Freeman's findings<sup>7</sup> of no false positive tests with a nonreactive positive OCT, compared to seven of 15 with a reactive positive test. Since the patients with a terminal CTG were not allowed to go into labor, comparison with data on them concerning a nonreactive positive OCT is not possible. However, a repetitive spontaneous decelerative pattern seems to indicate more reliably the fetus at risk than does the reactive positive OCT. Overstimulation with hypertonia or an oxytocin-induced abnormal contraction pattern might be one of the reasons for this difference.

# REFERENCES

- Visser, G. H. A., and Huisjes, H. J.: Diagnostic value of the unstressed antepartum cardiotocogram, Br. J. Obstet. Gynaecol. 84:321, 1977.
- Flynn, A. M., and Kelly, J.: Evaluation of fetal well-being by antepartum fetal heart monitoring, Br. Med. J. 1:936, 1977.
- 3. Ewing, D. E., Farina, J. R., and Otterson, W. N.: Clinical

- application of the oxytocin challenge test, Obstet. Gynecol. 43:563, 1974.
- Christie, G. B., and Cudmore, D. W.: The oxytocin challenge test, Am. J. Obstet. Gynecol. 118:327, 1974.
- Weingold, A. B., De Jesus, T. P. S., O'Keiffe, J.: Oxytocin challenge test, Am. J. OBSTET. GYNECOL. 123:466, 1975.
- Gauthier, R. J., Evertson, L. R., Paul, R. H.: Antepartum fetal heart rate testing. II. Intrapartum fetal heart rate observation and newborn outcome following a positive contraction stress test, Am. J. Obstet. Gynecol. 133:34, 1979.
- Braly, P., and Freeman, R. K.: The significance of fetal heart rate reactivity with a positive oxytocin challenge test, Obstet. Gynecol. 50:689, 1977.
- Emmen, L., Huisjes, H. J., Aarnoudse, J. G., et al.: Antepartum diagnosis of the "terminal" fetal state by cardiotocography, Br. J. Obstet. Gynaecol. 82:353, 1975.
- Visser, G. H. A., and Huisjes, H. J.: The meaning of the normal and pathologic antepartum cardiotocogram (CTG), 5th European Congress of Perinatal Medicine, Abstracts, Stockholm, 1976, Almqvist and Wiksell, p. 58.
- Kloosterman, G. J.: On intrauterine growth, Int. J. Gynaecol. Obstet. 8:895, 1970.

- Thomson, A. M., Billewicz, W. Z., Hytten, F. E.: The assessment of fetal growth, J. Obstet. Gynaecol. Br. Commonw. 75:903, 1968.
- 12. Jacobson, L.: Studies on acid-base and electrolyte components of human fetal and maternal blood during labour, Student litteratur, Lund, 1970, p. 84.
- Kubli, F., Rüttgers, H., Haller, Ü., et al.: Die antepartale fetale Herzfrequenz. II, Z. Geburtshilfe Perinatol. 176: 309, 1972.
- Wheeler, T., Cooke, E., and Murrills, A.: Computer analysis of fetal heart rate variation during normal pregnancy, Br. J. Obstet. Gynaecol. 86:186, 1979.
- Meyers, R. E., Muller-Heubach, E., and Adamsons, K.: Predictability of the state of fetal oxygenation from a quantitative analysis of the components of late deceleration. Am. J. Obstet. Gynecol. 115:1083, 1973.
- Sadovsky, E., Yaffe, H., and Polishuk, W. Z.: Fetal movement monitoring in normal and pathological pregnancy, Int. J. Gynaecol. Obstet. 12:75, 1974.
- 17. Jurgens-van der Zee, A. D., Bierman-van Eendenburg, M. E. C., Fidler, V. J., et al.: Preterm birth, growth retardation and acidemia in relation to neurological abnormality of the newborn, Early Hum. Dev. 2:141, 1979.

# First-trimester fetal chromosomal diagnosis using endocervical lavage: A negative evaluation

MARSHALL F. GOLDBERG, M.D., M.P.H.
ANDREW T. L. CHEN, Ph.D.
YOUNG W. AHN, M.D.
JOHN A. REIDY, Ph.D.
Atlanta, Georgia

A report in the literature indicated that fetal cells could be obtained by endocervical lavage during the first trimester of pregnancy and successfully cultured. This would allow prenatal diagnosis earlier in pregnancy than is currently possible with second-trimester amniocentesis. Therefore, we attempted to confirm these findings. Our results indicated that the cultured cells were maternal in origin. We disagree with interpretations of the data given in the initial report and conclude that first-trimester prenatal diagnosis is not feasible at this time. (Am. J. Obstet. Gynecol. 138:436, 1980.)

ALTHOUGH recent collaborative studies in the United States<sup>1</sup> and Canada<sup>2</sup> have established the relative accuracy and safety of second-trimester amniocentesis for prenatal diagnosis, the procedure still has significant drawbacks and complications. These can be attributed primarily to the late timing and invasiveness of the procedure.

Since amniocentesis generally cannot be done until the fourteenth to sixteenth week of gestation, and cell culture results usually require 3 to 5 weeks, vital genetic information about the fetus is not available until the seventeenth to twenty-first week of pregnancy. Should the fetus be abnormal and pregnancy termination desired, the abortion is delayed to a gestational period in which the maternal morbidity and mortality for such an operation is increased. Moreover, should the amniotic fluid cell culture fail to provide the needed information, the late timing of a second amniocentesis and the long time required for culture results may negate

From the Birth Defects Branch, Cancer and Birth Defects Division, Bureau of Epidemiology, Center for Disease Control; the Genetics Laboratory, Pathology Division, Bureau of Laboratories, Center for Disease Control,
Department of Health, Education and Welfare; and the Department of Gynecology and Obstetrics, School of Medicine, Emory University.

Received for publication July 7, 1980. Accepted July 28, 1980.

Reprint requests: Dr. Andrew T. L. Chen, Genetics Laboratory, Center for Disease Control, Atlanta, Ga. 30333. the feasibility and usefulness of a repeat study. In addition, potential complications resulting from the basic invasiveness of second-trimester amniocentesis are documented in the literature.

To improve upon second-trimester transabdominal amniocentesis as a diagnostic tool, one must have a technique which can be used in the first trimester and which avoids the complications mentioned. This technique should have also a high degree of accuracy and be as simple as possible. Alternatives to transabdominal amniocentesis, which have met some of these requisites, have been investigated in the past 10 years. These methods have consisted of recovering trophoblastic cells in the maternal circulation,<sup>3</sup> direct villus biopsies with a hysteroscope,4 blind transcervical aspirations of the fetal membranes,<sup>5</sup> and endocervical smears for sampling exfoliated fetal cells.<sup>6</sup> The relative simplicity and apparent safety of the last-mentioned method attracted much attention in the literature, but, unfortunately, mixed results emanating from a number of centers underscored its unreliability.6-13

Convinced that exfoliated trophoblast accumulated behind the cervical mucous plug at the level of the internal os, Rhine and associates<sup>14</sup> developed an antenatal cell extractor (ACE) to collect a sufficient number of cells for tissue culture and subsequent karyotyping. Rhine and associates' data indicated that first-trimester prenatal diagnosis might be feasible.

Encouraged by Rhine and associates' preliminary results, which could have a great impact on prenatal diagnosis, we undertook a pilot study specifically de-

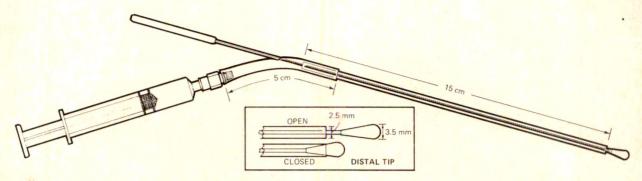


Fig. 1. The antenatal cell extractor (ACE).

signed to replicate their work and extend their findings. Our objectives were to obtain samples of exfoliated trophoblast by endocervical lavage, to grow the trophoblastic tissue in cell culture, and karyotype the cultured cells.

### Material and methods

Thirty patients who elected to undergo outpatient first-trimester abortion at Grady Memorial Hospital participated in the pilot study. Eighty percent were multigravidas; their age range was 18 to 28 years (mean = 23.2). Mean gestational age at the time of pregnancy termination was 10.5 weeks by examination (range, 8 to 13 weeks). None of the patients had an underlying medical or surgical illness, gave a history of habitual abortion, nor presented with manifestations of a threatened abortion. After the nature and purpose of the study, potential risks attendant on the endocervical lavage, and the specimens required were described to the patient, informed consent was obtained at least 1 day before the patient's scheduled abortion. Endocervical samples were collected immediately before the abortion in all cases. An appropriate sample of the products of conception was obtained after the abortion was completed (see below).

To obtain endocervical samples of exfoliated trophoblast, a replication of the antenatal cell extractor (ACE) devised by Rhine and associates14 was employed (Fig. 1). This device consisted of a clear plastic tube, 2.5 mm in diameter and 15 cm long. The proximal end of the tube was covered by a 5 cm plastic sleeve to which a Luer-Lok-type syringe adapter was attached. Running through the tube was a 0.7 mm metal rod which had a 3.5 mm plastic bulb secured to its tip. Pushing on the plunger handle projected the bulb forward, thus opening the tube; and pulling on the handle held the bulb against the distal end of the tube, thereby closing it. Hence, the ACE was closed during insertion in order to avoid the bacterial contamination of the cervical canal, opened at the internal os in order to obtain the speci-

men, and then closed again before being withdrawn through the contamination of the mucous plug. The ACE was gas sterilized before each use and maintained in a sterile container.

To obtain the specimen with the ACE, the patient was positioned on the operating table, prepared, and draped in the usual fashion for an outpatient vaginal operation. A gentle bimanual examination was then performed to determine the size of the uterus and its position; the physician estimated the size of the uterus in order to confirm gestational age. A sterile speculum was subsequently inserted into the vagina, and the ectocervix was cleansed with Betadine solution. Next, the anterior lip of the cervix was grasped with a singletoothed tenaculum; a uterine sound was then gently passed into the cervical canal to ascertain its direction and measure the distance to the internal os. A 5 cc syringe filled with saline solution was attached to the adapter on the proximal end of the ACE, and the entire tube was filled with saline solution. The 5 cc syringe was refilled so that it contained 5 cc of sterile saline solution. The distal tip of the ACE was inserted to the level of the internal os; when the bulb just passed the constriction of the os, the ACE plunger was pushed forward 1 or 2 mm. Sterile saline solution was expelled into the area just above the os and then withdrawn into the ACE tip by retraction of the syringe plunger. The tube itself was then closed by pulling the plastic bulb back, and the entire ACE was withdrawn from the cervix. Two specimens per patient were collected since this increased the number of cells obtained and minimized maternal decidual contamination. 14 Each specimen was expelled into a sterile 15 cc conical centrifuge tube which contained a solution of nutrient medium plus penicillin, streptomycin, and Fungizone. The inside of the ACE was then rinsed with 5 cc of the nutrient medium-antibiotic solution; this fluid was collected in a separate sterile container. All three specimens were immediately transported to the Genetics Laboratory at the Center for Disease Control (CDC).

438 Goldberg et al.

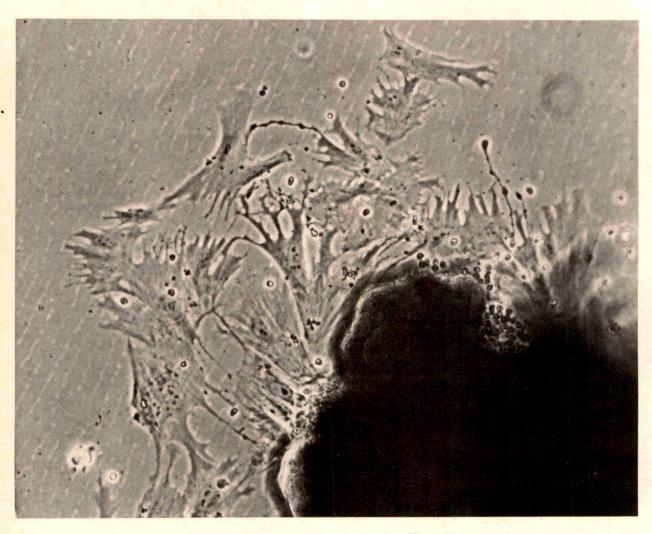


Fig. 2. Cellular outgrowth from explant in ACE specimen.

After each pregnancy was terminated, the products of conception were examined and a specimen was taken. These samples were also transported in a solution of antibiotics and nutrient medium to the laboratory for cell culture and analysis.

Upon arrival at the laboratory, the contents of the specimen tubes were centrifuged at 1,000 rpm for 5 minutes, the supernatant was discarded, and the tissue was transferred via a sterile pipette into Falcon flasks which contained McCoy's 5 A medium and antibiotics; sterile curved scissors were used to mince any large pieces of tissue into very fine fragments. The Falcon flasks which contained the tissue were then incubated at 37° C with McCoy's 5 A medium supplemented with 15% fetal-calf serum and antibiotics.

The cultures were examined daily with a phasecontrast inverted microscope. As soon as enough cells were growing, they were harvested by standard cytogenetic techniques. The cells were then Q-banded with quinacrine dihydrochloride. Metaphase spreads were scored for chromosome number and sex.

### Regulte

Using the ACE, we obtained cells of trophoblastic origin, as evidenced by the chorionic villi that we saw on cytologic examination of the lavage fluid. Growth of at least two different cell types was observed, either in isolated colonies or emanating from typical trophoblastic explants (Fig. 2).

All ACE specimens which grew sufficiently were harvested for determination of chromosomal sex by Q-banding. In the first two cases, because the ACE specimens were found to have female chromosome constitutions, maternal lymphocytes were also examined. No conclusive chromosomal polymorphism differences between the ACE cells and maternal cells

were observed. Since the interpretation of polymorphisms is subjective, and therefore possibly unconsciously biased, we decided to concentrate on those cases in which the fetal tissue was male (46,XY). In these informative cases, the interpretation was straightforward: female ACE cells (46,XX) would be of maternal origin, whereas male ACE cells (46,XY) would be of fetal origin.

We successfully cultured male fetal tissue from 12 patients. In nine of these cases, the ACE specimen grew sufficiently for chromosome analysis. In all nine cases the chromosomes of the ACE cells were female. This clearly demonstrated the maternal origin of the ACE specimen in each informative case.

# Comment

In an early phase of the work of Rhine and associates,14 samples were obtained from first-trimester patients, 24 hours prior to therapeutic abortion. Cell growth was observed in 18 of 21 samples, and five of these grew well enough for a study of chromosomes. Maternal lymphocytes and endocervical samples were scored for Q-band polymorphisms and compared. A difference in a chromosomal polymorphism in the two samples was interpreted as the paternal contribution to the trophoblast. In the five pairs of samples scored, a difference was noticed in every instance.

In a later phase of their work, Rhine and associates14 immediately repeated the sampling procedure for each patient. This increased the volume of tissue obtained and increased the yield of mitoses that could be scored. Rhine and his group observed growth in 12 of 13 firsttrimester patients. In 11 of the 12 successful cultures, Rhine and associates observed chromosome polymorphisms which differed from those of the maternal lymphocytes. This was interpreted to mean that the ACE cells were of fetal origin in these 11 cases.

We think that our inability to demonstrate a male karyotype among the cells retrieved with the ACE casts serious doubt upon the validity of Rhine and associates' findings. Even though it is true that polymorphic markers distinguished 11 of 12 karyotypes in their last series from obvious maternal cell contamination, Rhine and his co-workers should have obtained at least one typically male karyotype, on the basis of probability

The chance that all 11 informative cases were female is extraordinarily remote. The probability of such an event is (1/2)11 or 0.000488. If we include the five informative cases from preliminary study, the probability shrinks to (1/2)16 or 0.000015. Rhine and associates state that the failure to observe a Y chromosome in their ACE cultures could be due to the poor quality of the metaphases obtained. Therefore, they may have had some males in their series, and the probability calculations above would not apply. However, if the quality of their preparations was so poor that the Y chromosome could not be distinguished, we doubt that polymorphisms could have been reliably scored.

This failure to culture fetal cells from the ACE specimen does not rule out the possibility of sampling fetal tissue by noninvasive means during the first trimester. It merely means that we, and perhaps Rhine and associates, have failed to do so.

Recently, Rhine and Milunsky<sup>15</sup> reported the growth of male cells from an ACE specimen obtained at 9 weeks' gestation. They did not present data to indicate the reliability of obtaining fetal cells with this procedure. We suggest that the promising results of Rhine and associates14, 15 must be interpreted cautiously. We hope that this method can be developed into a reliable diagnostic procedure.

We wish to thank Ms. Linda Shulin for her able work in the laboratory.

# REFERENCES

1. National Institute of Child Health and Human Development, National Registry for Amniocentesis Study Group: Midtrimester amniocentesis for prenatal diagnosis. Safety and accuracy, J.A.M.A. 236:1471, 1976.

2. Simpson, N. E., Daillaire, J. R., Miller, J. R., Siminovitch, L., Hamerton, J. L., Miller, J., and McKeen, C.: Prenatal diagnosis of genetic disease in Canada: Report of a collaborative study, Can. Med. Assoc. J. 115:729, 1976.

- 3. Raafat, M., Brayton, J. B., Apgar, V., and Borgaonkar, D. S.: A new approach to prenatal diagnosis using trophoblast cells in the maternal blood, Birth Defects 11:295, 1975.
- Kullander, S., and Sandahl, B.: Fetal chromosome analysis after transcervical placental biopsies during early pregnancy, Acta Obstet. Gynecol. Scand. 52:355, 1973.
- 5. Department of Obstetrics and Gynecology, Tietung Hospital of Anshan Iron and Steel Company, Anshan: Fetal sex prediction by sex chromatin of chorionic villi cells during early pregnancy, Chin. Med. J. 1:117, 1975.
- 6. Rhine, S. A., Cain, J. L., Cleary, R. E., Palmer, C. G., and Thompson, T. F.: Prenatal sex detection with endocervical smears: Successful results utilizing Y-body fluorescence, Am. J. Obstet. Gynecol. 122:155, 1975.
- 7. Shettles, L. B.: Use of the Y chromosome in prenatal sex determination, Nature 230:52, 1971
- Warren, R., Sanchez, L., Hammond, D., and McLeod, A.: Prenatal sex determination from exfoliated cells found in cervical mucosa, Am. J. Hum. Genet. 24:29a, 1972.
- 9. Bobrow, M., and Lewis, B. V.: Unreliability of fetal sexing using cervical material, Lancet 2:486, 1971.
- 10. Goldstein, A. J., Lukesh, R. C., and Ketchum, M.: Pre-

440 Goldberg et al.

October 15, 1980
Am. J. Obstet. Gynecol.

 natal sex determination by fluorescent staining of the cervical smear for the presence of a Y chromosome: An evaluation, Am. J. Obstet. Gynecol. 115:866, 1973.

- evaluation, Am. J. Obstet. Gynecol. 115:866, 1973.

  11. Manuel, M., Park, J. J., and Jones, H. W.: Prenatal sex determination by fluorescent staining of cells for the presence of Y chromatin, Am. J. Obstet. Gynecol. 119:853, 1974.
- 12. Varner, R. E., Younger, J. B., Finley, S. C., and Finley, W. H.: Fluorescent Y bodies in cells from endocervical smears for prenatal sex detection, Clin. Res. 25:74A, 1977
- 13. Amankwah, K. S., and Bond, E. C.: Unreliability of prenatal determination of fetal sex with the use of Y-body fluorescence in midcervical smears, Am. J. Obstet. Gynecol. 130:300, 1978.
- Rhine, S. A., Palmer, C. G., and Thompson, T. F.: A simple alternative to amniocentesis for first-trimester prenatal diagnosis, Birth Defects 13:231, 1977.
- Rhine, S. A., and Milunsky, A.: Utilization of trophoblast for early prenatal diagnosis, in Milunsky, A.: Genetic Disorders and the Fetus, New York, 1979, Plenum Press, p. 597

# Placental size during early pregnancy and fetal outcome: A preliminary report of a sequential ultrasonographic study

HENK J. HOOGLAND, M.D.

JELTE DE HAAN, M.D.\*

CHESTER B. MARTIN, Jr., M.D.

Nijmegen, The Netherlands

Placental growth during pregnancy was studied serially by ultrasonographic measurement of placental area in 50 primigravid women. Placental area at a menstrual age of 150 days was compared to infant birth weight. Small placental area at a menstrual age of 150 days was significantly related to low infant birth weight (<tenth percentile of birth weight for gestational age). A "warning limit" of placental area at midpregnancy was calculated. If placental area was equal to or smaller than this limit of 187 sq cm, six of nine patients (67%) compared to four of 41 subjects with larger placentas (p < 0.01) were delivered of a small-for-gestational age baby. Ultrasonographic placental area measurement in midpregnancy thus appears to be of prognostic value in identifying pregnancies at high risk for the subsequent occurrence of fetal growth retardation. (AM. J. OBSTET. GYNECOL. 138:441, 1980.)

THE ASSOCIATION between low infant birth weight for gestational age and small placental size has been noted by many authors, especially in cases where the fetal growth retardation is of the asymmetric or intrauterine malnutrition type. The literature also contains many reports concerning antepartum detection of fetal growth retardation by means of ultrasonographic measurement of the fetus; however, relatively little attention has been directed to the antepartum assessment of placental size and its consequences for fetal growth. We report here a prospective study relating placental area measured ultrasonically at midgestation to the subsequent birth weight categories of the infant.

# Methods and subjects

Ultrasonographic placental localization was performed in 105 primigravid women during the first half

> From the Department of Obstetrics and Gynecology, Sint Radboudziekenhuis, Medical Faculty, Catholic University.

Received for publication February 1, 1980.

Revised May 30, 1980.

Accepted June 30, 1980.

Reprint requests: H. J. Hoogland, M.D., Department of Obstetrics and Gynecology, Ziekenhuis Sint Annadal, State University Limburg, Maastricht, The Netherlands.

\*Present address: Department of Obstetrics and Gynecology, Ziekenhuis Sint Annadal, Medical Faculty, State University, Maastricht, The Netherlands. of pregnancy. In 52 of these women, the placenta was located anteriorly. One subject was subsequently excluded because of the presence of a twin pregnancy, and another withdrew from the study. The remaining 50 women were studied serially throughout pregnancy.

Placental scans were obtained with a Diasonograph Model NE 4200, connected to a gray-scale scan converter. Placental area was calculated from serial sonograms obtained at 1 cm intervals in transverse and longitudinal directions. In the sonograms showing the greatest extent of the placenta in each direction, the length of the chorionic surface was measured by means of a curvimeter (Ahrend). The product of the greatest chorionic surface lengths in transverse and longitudinal directions was used as an approximation of placental area. To test the reproducibility of the method, 194 duplicate measurements of placental area were made. A mean relative error of 3% was found with regard to each dimension. The measurement procedure has been described in greater detail elsewhere.

The pregnancies of the study subjects were dated on the basis of menstrual data. In cases where an uncertainty in the menstrual age of more than 7 days was present, fetal crown-rump length or biparietal diameter was measured at least twice during the first half of pregnancy and menstrual age was calculated from these measurements.

A menstrual age of 150 days was selected for the

investigation of the possible predictive value of midpregnancy placentometry. This time represents very nearly the average midpoint of gestation (133 days) augmented by mean preovulatory phase duration (14

Placental area was actually measured at a menstrual age of 150 days in only one subject. In the other subjects, placental area at 150 days' menstrual age was calculated by two methods. By the simple method, placental area at 150 days was obtained by linear interpolation from the last measurement before day 150 (range 108 to 149 days) and the first measurement after day 150 (range 151 to 198 days) (n = 49). In the second method, the value for placental area at 150 days was based on the linear regression analysis of each individual placental growth curve determined from all measurements (range 3 to 5) obtained up to 175 days (n = 37). The mean difference between the results of the two methods of calculation was 1 sq cm (±10 SD cm, n = 37). Since the results of the two methods of calculation did not differ significantly (p >> 0.1, Student's one-sample test) or systematically, the more simple interpolation of placental area from the measurements closest on either side of 150 days' menstrual age was employed in the final calculations for all subjects.

The birth weight percentile for gestational age at delivery<sup>2</sup> was used as the measure of pregnancy outcome.

### Results

The earliest satisfactory measurement of placental area could be done between the ninth week and the eleventh week of gestation. Before this period, the boundaries of the definitive placenta could not be distinguished from the decidua and chorion frondosum. The smallest placental area measured in our material was 40 sq cm at 71 days. From this time onward, placental area increased rapidly in most cases.

The subsequent distribution of infant birth weights for the 50 pregnancies studied serially was: appropriate for gestational age (birth weight ≥tenth, ≤ninetieth percentiles), 38 infants; small for gestational age (<tenth percentile), 10 infants; and large for gestational age (>ninetieth percentile), two infants.

Comparison of the ultrasonically determined placental area at 150 days with the subsequent birth weight of the infant revealed a mean placental area of 188 ± 50 (SD) sq cm when the birth weight was below the tenth percentile for gestational age (n = 10) and 235 ± 35 sq cm when the birth weight was between the tenth and ninetieth percentiles (n = 38). This difference is statistically significant (p = 0.001, Student's t test). The two macrosomic fetuses had placental areas at 150 days of 210 and 296 sq cm.

The ultrasonically measured placental areas at 150 days of the 38 normally grown infants appeared to be drawn from a normal Gaussian distribution. This was substantiated by the normality tests of Shapiro and Wilk<sup>3</sup> (p >> 0.1 by each test). Further, the values for skewness (0.21) and kurtosis (-0.49) were small. On the basis of a Gaussian distribution, it can be calculated with a confidence level of 90% that at least 5% of the placental area values of women with infants who are appropriate for gestational age will be equal to or less than 187 sq cm at a menstrual age of 150 days. This value thus represents a one-sided guarantee tolerance limit and can be used as a warning limit. In the present study population, six of nine subjects with placental area  $\leq 187$  sq cm at 150 days compared to four of 41 subjects with placental areas greater than the calculated warning limit subsequently were delivered of small-for-gestational age infants. This difference is statistically significant (p < 0.01, chi-square test).

# Comment

Ultrasonographic measurement of the placenta during pregnancy has been described by Holländer and Mast,4 Hellman and associates,5 and Bleker and associates.6 In these studies non-gray-scale compound scan techniques were used, and in these methods the margins of the placenta are not always distinguishable. None of the studies was prospective with regard to fetal outcome. In our prospective study, in contrast to those of the previously mentioned authors, we used grayscale techniques and only measured the surface of the placental disk because of the restricted accuracy of placental thickness measurements.1

For a reliable study of the placenta by ultrasound throughout pregnancy, the placenta must be located on the anterior wall of the uterus, so that artifacts caused by the acoustic shadows of overlying fetal parts are avoided. Application of this selection criterion in the present study resulted in exclusion of one half of the potential subjects.

The most interesting part of the placental growth curve is found during early pregnancy. During this period, placentas located on the posterior wall of the uterus often can be measured because overlying fetal parts during early pregnancy cause only slight artifacts. Thus, it is possible that placental growth can be monitored during early pregnancy irrespective of placental location. Until the applicability of ultrasound measurement techniques to posteriorly located placentas is directly tested, however, the possibility remains that this screening procedure may be limited to the 40% to 50% of gravid subjects with anterior placentas.

In the present study, six of nine subjects with placen-

1

tal areas of 187 sq cm or less at 150 days eventually were delivered of small-for-gestational age babies. In a larger, unselected population, the predictive efficiency would probably be somewhat smaller.

If the birth weight distribution tables are appropriate for the population under study, the ratio of low birth weights to normal birth weights in a large population will be 1:8. A higher ratio of low to normal birth weights (10:38) was observed in the study group. Applying observed incidence figures for the occurrence of placentas below the calculated warning limit to a larger unselected population, one can estimate that approximately half of pregnancies where the placental area by our method is ≤ 187 sq cm at 150 days will end in the delivery of a small-for-gestational age infant. This still

represents a fivefold increase in the incidence of low birth weight.

Our findings reaffirm the frequently noted association between small placentas and small-for-dates babies. Although serial fetal measurements were not performed in the present study, ultrasonographically evident fetal growth retardation does not usually appear until after the end of the second trimester. Thus, the present findings also suggest that placental growth retardation can be demonstrated in advance of fetal growth retardation. Although the number of subjects in the present study is too small to allow definite conclusions to be drawn, the results clearly indicate that a larger, prospective investigation of the value of ultrasonographic placentometry is warranted.

# REFERENCES

- Hoogland, H. J.: Ultrasonographic aspects of the placenta, Alphen a/d Rijn, The Netherlands, 1980, Staffeu.
- Kloosterman, G. J.: De voortplanting van de mens, Haarlem, The Netherlands, 1977, Centen, p. 82.
- Shapiro, F. S., and Wilk, M. B.: An analysis of variance test for normality, Biometrika 52:591, 1965.
- 4. Holländer, H. J., and Mast, H.: Intrauterine Dickenmes-
- sungen der Plazenta mittels Ultraschalls bei normalen Schwangerschaften und bei Rh-Incompatibilität, Geburtshilfe Frauenheilkd. 28:662, 1968.
- Hellman, L. M. Kobayashi, M., Tolles, W. E., and Cromb, E.: Am. J. Obstet. Gynecol. 108:740, 1970.
- Bleker, O. P., Kloosterman, G. J., Breur, W., and Mieras,
   D. J.: Am. J. Obstet. Gynecol. 127:657, 1977.

# Mechanisms of beat-to-beat variability in the heart rate of the neonatal lamb

# I. Influence of the autonomic nervous system

MARCELO ZUGAIB\*
ALAN B. FORSYTHE
BAHIJ NUWAYHID\*\*
STEPHEN M. LIEB
KHALIL TABSH
RISTO ERKKOLA\*\*\*
ETSUO USHIODA\*\*\*
C. R. BRINKMAN III
N. S. ASSALI
Los Angeles, California

The contributions of the intrinsic, beta-adrenergic, and cholinergic systems to the mechanisms of beat-to-beat variability of the heart rate were investigated in chronically instrumented, unanesthetized newborn lambs from the first week to the eighth week of neonatal life. During this period of neonatal growth, the resting heart rate decreased spontaneously every week; the decrease was not related to alterations in the sympathetic and parasympathetic tones but rather to changes in the intrinsic mechanisms of heart rate control. Despite the weekly decrease in the resting heart rate of the neonatal lamb, the long and short-term beat-to-beat variabilities did not change significantly. This finding suggests an absence of a significant influence of the intrinsic mechanisms of heart rate control on the genesis of beat-to-beat variability. The results obtained with the various modes of adrenergic and cholinergic blockades and stimulation seem to indicate that the autonomic nervous system contributes significantly to the appearance of beat-to-beat variability. However, the influences of the adrenergic and cholinergic systems differ from week to week of neonatal growth and the patterns of changes are not the same for the long-term and short-term variabilities. The implication of these studies in terms of physiologic and hemodynamic significance of beat-to-beat variability in heart rate is discussed. (Am. J. Obstet. Gynecol. 138:444, 1980.)

THE HEART RATE (HR) has been used as an index of fetal and neonatal well-being for many years. In the

From the Departments of Obstetrics and Gynecology and Biomathematics, University of California, Los Angeles School of Medicine.

Supported by Grants HL 01755 and HL 13634 from the National Institutes of Health.

Received for publication September 24, 1979.

Revised June 23, 1980.

Accepted June 30, 1980.

Reprint requests: Bahij Nuwayhid, M.D., UCLA School of Medicine, Department of Obstetrics and Gynecology, Los Angeles, California 90024.

past, episodes of fetal bradycardia or tachycardia were sufficient to alert physicians of impending fetal problems. With the advances in electronic technology that have occurred during the past decade, however, fetal and neonatal HR monitoring has become considerably more complex. Various tests based on variations in HR

\*Fellow in Reproductive Physiology, sponsored in part by "Conselho Nacional de Desenvolvimento Científico e Tecnologico", Brazil.

\*\*Recipient of Research Career Development Award HD

\*\*\*National Institutes of Health Fogarty Fellow in Reproductive Physiology.

Table I. Details of experiments

Experimental drug	No. of tests	Dose/kg	Site of action
Atropine	40	200 μg	Muscarinic receptors Adrenergic receptor blocker Muscarinic plus adrenergic
Propranolol	41	200 μg	
Atropine plus propranolol	42	200 μg of each	
Isoproterenol	49	0.05 μg	receptor blockers
	54	0.10 μg	Adrenergic receptor stimulant

patterns have been devised which are thought to provide information on fetal conditions in suspected high-risk pregnancies. 1-6

The aspect of fetal HR monitoring that has created more interest in recent years pertains to the instantaneous variability that is observed from beat to beat. Various investigators believe that monitoring the beatto-beat variability in the baseline HR provides a more accurate assessment of the presence or absence of fetal distress. 1-6 Although very little effort has been made to investigate the mechanisms and the hemodynamic consequences of the beat-to-beat variability, most authors believe that it results from interactions between the sympathetic and parasympathetic components of HR control.

The present studies were designed to investigate some of the mechanisms that may underlie the instantaneous beat-to-beat variabilities in the HR of the neonatal lamb. We selected the neonate instead of the fetus for the following reasons: (1) it is simpler and considerably more accurate to monitor the HR and its instantaneous variability for a long period of time during the neonatal period than during intrauterine life; many of the technical difficulties and interfering variables that are encountered in fetal studies can be minimized or eliminated. (2) We have previously shown that the HR of the newborn lamb changes spontaneously throughout the first 8 weeks of the neonatal period and that these changes are related to modifications of the intrinsic mechanisms of HR control rather than to the sympathetic and parasympathetic systems.7 By observing the beat-to-beat variability in a spontaneously changing HR, we thought that we might be able to shed light on the contributions of these three components of heart rate control to this phenomenon. (3) The effectiveness of a given mode of blockade or stimulation of any component of the autonomic nervous system is more assured and more predictable in the neonate than in the fetus, mainly because of the absence of vascular shunts and the low resistance system of the umbilicoplacental circulation.

This report deals with the role of the beta-adrenergic, cholinergic, and intrinsic systems in the genesis of beat-to-beat variability.

# Material and methods

Animal preparation. Seven near-term ewes of mixed breed with dated gestational ages were allowed to deliver spontaneously in our animal care facilities; hence, the exact age of each lamb was known. The lambs were housed with their mothers so that normal lactation could be accomplished until they were able to eat the same diet given to the ewes and drink on their own during the period of observation.

Each lamb was allowed a 3-day period of neonatal adjustment before it was subjected to operation. Chronic instrumentation of the lamb was accomplished under aseptic conditions by techniques previously reported.7, 8 Briefly, with the use of local infiltration anesthesia (1% Xylocaine), polyvinyl catheters were placed in the carotid artery and jugular vein. The carotid catheter served for measurement of systemic arterial pressure and HR and the jugular catheter was used for intravenous drug administration. In addition, two electrodes made of stainless steel or silver loops 5 mm in diameter were implanted subcutaneously on the animal's chest, one over the precordial area and the other at a distance of 15 cm over the back of the animal (this electrode position was found by trial and error to provide the best R-wave record with minimal artifacts).

A postoperative recovery period of 48 hours was allowed before the studies were begun. The lamb's activities, feeding habits, respiration, muscle tone and weight were checked daily while hemoglobin, hematocrit, blood respiratory gases, and pH were analyzed at frequent intervals. The same lamb was studied from the first week through the eighth week of neonatal life. Circulatory functions, including HR variability in the resting state, were recorded daily for the 8 weeks of the observation period. These data were used to calculate the spontaneous changes in the resting HR and its beat-to-beat variabilities throughout this period of neonatal growth.

Autonomic antagonists and the agonist used in these experiments, including the dosage, site of action, and number of tests, are listed in Table I. The number of experiments per week for each drug varied from five to eight. The doses used were chosen as being the most effective in blocking beta-adrenergic and cholinergic

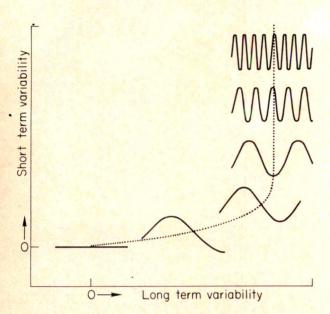


Fig. 1. Schematic representation of computer simulation for the long- and short-term variabilities. See text for further details.

receptors and were based on our previous doseresponse curves constructed for these agents during identical periods of neonatal development.<sup>7</sup>

A weekly study schedule was established for each lamb and no more than one test with an autonomic antagonist or agonist was performed in a given day. This schedule permitted collection of data on the effects of all of the agents listed in Table I from the same animal every week.

The experimental protocol consisted of the following periods: (1) a control period lasting 30 to 40 minutes, during which the animal stood quietly in its cage while recording of the resting HR and arterial pressure was made continuously; (2) a testing period, during which the agent selected for assessing a given autonomic activity was administered in predetermined doses through the jugular vein in single bolus injections. Recordings of HR and arterial pressure were made continuously after each injection for about 2 to 3 hours; the average reading of 4 to 5 minutes during maximum effects of the drug was taken as the response to that test<sup>1</sup>; (3) a recovery period of 30 to 40 minutes, which terminated the experiment for that day. During all of these periods, the lamb stood quietly and was prevented from sitting or moving by a sling support that allowed full weight bearing on all four extremities.

Criteria for defining and calculating heart rate variability. Since there are no uniform criteria among workers in this field on how to calculate or express HR variability, 1-6, 9 we arbitrarily decided on the following methodology and definitions:

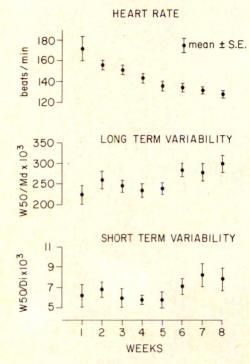


Fig. 2. Average (±1 SE) of the weekly values of the resting HR with corresponding values for long- and short-term variabilities from the first week to the eighth week of neonatal life. Resting HR decreased weekly throughout the neonatal period, but LTV and STV did not change significantly.

- 1. For the purpose of electrocardiographic recording of the R-wave intervals, the paper speed was set at 5 cm/sec.
- 2. The distances between successive R-R intervals were measured (in milliseconds) with a manual digitizer system coupled to a computer.
- 3. Three to four periods of 128 R-R intervals were measured during the control period prior to drug injection and a similar number of readings were collected during the maximum effects of a given drug (the number 128 was arbitrarily selected after several trials with lower and higher numbers).
- 4. HR represents the number of beats per minute for each period of observation (128 intervals). The instantaneous HR (Y) at each interval was first calculated by dividing the total number of milliseconds per minute  $(60 \times 10^3)$  by the specific interval in milliseconds (X<sub>i</sub>):

$$Y = \frac{60 \times 10^3}{X_i}.$$

The mean HR was then calculated from the sum of all Ys  $(\Sigma Y)$  and the number of periods (N):

$$HR = \frac{1}{N}\Sigma Y.$$

+60 +40 +20

FROM CONTROL (beats/min)

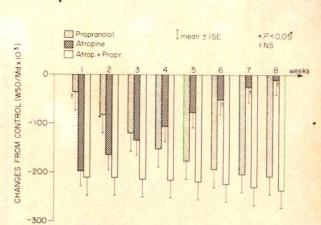
CHANGES - 20

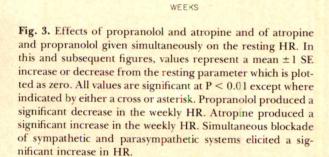
-40

Propranolol

Atrop.+Propr

M Atropine





I mean ± ISE

6

5. Long-term variability (LTV) was defined as the variability in the baseline HR that occurred during each entire period of observations (128 intervals). It was calculated by the formula:

LTV (W50/Md) = 
$$\frac{1}{N}\Sigma|X_1 - Md|/Md$$

where X<sub>i</sub> equals each R-R interval and W50/Md represents a calculated median.

Each R-R interval (Xi) was subtracted from the median and the absolute value of all these deviations was summed  $\Sigma \mid X_i - Md \mid$  and then divided by the number of intervals (N). This gives an estimate of the average deviation from the median during the entire period of 128 intervals (the median was used instead of the mean because it proved to be a more robust measure of variability10).

6. Short-term variability (STV) was defined as the variability in HR that occurred between two consecutive intervals and was calculated by the formula:

STV 
$$(W50/D_i) = \frac{1}{N-1} \Sigma |D_i - Md|$$

where

$$D_{i} = \frac{|X_{i} + 1 - X_{i}|}{(X_{i} + 1 + X_{i})}$$

and Xi, W50, and Md are the same symbols as stated above. Since STV reflects variability between two consecutive intervals, the number of samples (N) represents the number of intervals minus one (N-1). As

Fig. 4. Effects of propranolol, atropine, and simultaneous atropine and propranolol on LTV. Beta-adrenergic blockade produced a consistent decrease in LTV, the magnitude of which increased with neonatal growth. Parasympathetic blockade also produced a decrease in LTV, the magnitude of which decreased with growth. Pharmacologic denervation of the heart produced a marked fall in LTV, the magnitude of which was the same throughout the neonatal period.

with the LTV calculations, the deviations from the median rather than from the mean were selected for the reasons already explained.

For statistical treatment of the data, each animal was used as its own control. The values collected in the resting state during the control period prior to drug injections and during the peak of drug action were submitted to an analysis of variance to account for the differences between animals, weight, drug effects, and age as well as to assess the statistical significance of the differences.

Computer simulation. In order to test our methods of calculating long- and short-term variabilities and to assess the versatility of the formula to respond to changes in frequency and amplitudes of a given cycle, we performed computer analyses on a simulated heart rate in which frequency and amplitudes could be altered independently or simultaneously while we observed the behavior of the long- and short-term variabilities.

# Results

Conditions of the animals. All lambs had recovered from operation and had resumed their normal activities and feeding habits prior to the initiation of the studies. The resting values for HR, blood pressure, hemoglobin, hematocrit, pH, and blood respiratory gases were within the ranges of data previously observed for newborn lambs of this age in our laboratories.7, 8

Computer simulation. The results obtained from the computer simulation are presented in Fig. 1. LTV was

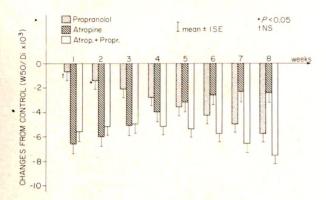


Fig. 5. Effects of propranolol and atropine and of atropine and propranolol given simultaneously on STV. Beta-adrenergic blockade produced a decrease in STV, the magnitude of which increased with neonatal age. Parasympathetic blockade elicited a significant decrease in STV, the magnitude of which diminished with neonatal growth. Pharmacologic denervation produced a marked and constant decrease in STV.

zero at a fixed HR. It increased slowly with the number of HR cycles up to 1½ cycles per minute but then became constant irrespective of the number of cycles per unit of time (Fig. 1). LTV, however, varied at all frequencies with changes in the amplitude of the cycle. Thus, at frequencies higher than 1½ cpm the changes in LTV reflected amplitude rather than frequency shifts.

STV increased in value with the number and amplitude of the cycles in heart rate up to half of the number of intervals studied (Fig. 1).

The results of the computer simulation indicated that: (1) the formulas used for calculating LTV and STV were versatile enough to detect minor changes in HRs of different frequencies and amplitudes; (2) the range was not a good way to characterize variability; and (3) the median was better than either the mean or the standard deviation for calculating variability since it proved to have stronger immunity to noise and other artifacts.

Resting HR and its variability during neonatal growth. In the upper panel of Fig. 2 the weekly values for the resting control HR observed during the 8 weeks of neonatal life are presented. In the lower two panels the corresponding weekly values for the LTV and STV in the resting HR during the same period of neonatal growth are presented.

The resting HR of the newborn lamb decreased progressively every week during the first 8 weeks of neonatal life. The average HR during the first week was 175 bpm and decreased to an average of 128 bpm during the eighth week (Fig. 2). These changes were similar to those previously reported for a similar group of newborn lambs.<sup>7</sup>

Both the LTV and STV of the resting HR changed inconsistently and insignificantly from week to week during neonatal growth (Fig. 2).

Effects of autonomic antagonists on the resting HR and variabilities. In Fig. 3 data are presented on the changes in the resting weekly HR observed after: (1) cholinergic blockade with atropine, (2) beta-adrenergic blockade with propranolol, and (3) acute pharmacologic denervation of the heart with simultaneous administration of atropine and propranolol. The significance of the figures presented for each week was related to the control values observed prior to the tests on that week, not to the magnitude of the responses in subsequent weeks.

Cholinergic blockade with atropine produced a consistent tachycardia without any significant change in the arterial pressure; the magnitude of the tachycardia decreased progressively with the growth of the animal between 1 and 8 weeks of age. During the first week, for instance, the increase in HR after atropine averaged about 55 bpm, whereas the same dose produced an average increase of only 25 bpm during the eighth week. The statistical analysis showed that the HR responses to atropine in relation to control were significant for each week, but the differences between subsequent weeks were significant only when the first 2 weeks were compared to the last week (Fig. 3).

Beta-adrenergic blockade with propranolol produced a bradycardia without significantly changing the arterial pressure; the magnitude of the bradycardia also decreased with the growth of the animal (Fig. 3). During the first neonatal week, the decrease in HR after propranolol averaged 23 bpm, whereas during the eighth week, it averaged only about 8 bpm. While the weekly response in relation to control HR was significant, only the difference between the first 2 weeks and the last week was significant.

Pharmacologic denervation of the neonatal heart increased the HR consistently without changing the arterial pressure; the HR increment, however, decreased somewhat with neonatal growth (Fig. 3).

In Fig. 4 the changes in LTV of the neonatal HR that occurred each week after cholinergic and beta-adrenergic blockade as well as after pharmacologic denervation are presented. Cholinergic blockade with atropine produced a decrease in LTV, the magnitude of which diminished with the growth of the newborn lamb. For instance, during the first week of neonatal life, LTV decreased about 200 U, following atropine, whereas it did not change significantly following the injections of the same doses during the last 3 weeks of the period of observation (Fig. 4).

Beta-adrenergic blockade, on the other hand, de-

creased LTV but the pattern of changes was opposite to that observed after cholinergic blockade (Fig. 4). During the first week, for instance, propranolol decreased LTV by about 35 U, whereas during the eighth week of neonatal life, the decrease produced by the same agent given in the same dosage exceeded 200 U (Fig. 4).

Pharmacologic denervation of the heart elicited an average decrease in LTV exceeding 200 U; the decrease was the same throughout the 8 weeks of neonatal life (Fig. 4).

In Fig. 5, the changes in STV following the various modes of autonomic blockade are presented. Cholinergic blockade with atropine also decreased the STV and the decrement was progressively smaller with the growth of the newborn animal.

Beta-adrenergic blockade likewise produced a decrease in STV, but the magnitude of the decrement increased with neonatal growth.

Pharmacologic denervation produced a significant decrease in STV which was of the same magnitude throughout the 8 weeks of neonatal growth (Fig. 5).

Effects of beta-adrenergic stimulation. In Fig. 6 the data on the effects of beta-adrenergic stimulation with two different doses of isoproterenol (0.05 and 0.10 μg/kg) on the resting HR and its variability throughout the neonatal period are presented.

The smaller dose of isoproterenol increased the resting HR by an average of about 25 bpm, whereas the larger dose increased it by an average of 60 bpm. Such responses were the same throughout the 8 weeks of observation (Fig. 6). The arterial pressure decreased by about 5% with the smaller dose and 8% with the larger

The smaller dose of isoproterenol increased LTV by about 200 U. The increment was the same throughout the 8 weeks.

The larger dose produced inconsistent changes in the LTV during the first 2 weeks; it did, however, increase it consistently and significantly during the last 5 weeks (Fig. 6).

The changes produced by both doses of isoproterenol in STV were inconsistent, decreasing during the first 2 weeks and increasing during the remaining weeks (Fig. 6).

# Comment

Development of HR control. Before we attempt to provide a meaningful interpretation to the data obtained from these studies, it would be appropriate to review briefly our present knowledge pertaining to the development of HR control.

Under normal circumstances, the HR is established

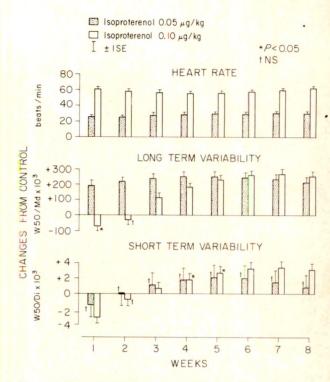


Fig. 6. Effects of different degrees of beta-adrenergic stimulation with isoproterenol on HR, LTV, and STV. HR increased significantly after isoproterenol and the increment was the same throughout the neonatal period. LTV also increased with beta-adrenergic stimulation but STV changed inconsistently.

by the periodic and automatic discharge of excitatory impulses emanating from the sinoatrial nodes. 11-13 It is well established that one of the most important properties of cardiac tissue and the first to develop in the embryonic stage is automaticity, i.e., the ability to beat rhythmically without external stimuli. The pacemaker centers of the sinoatrial and atrioventricular nodes are capable of maintaining cardiac automaticity for a long time after the heart has been totally denervated or surgically excised.11-13 The HR of the adult animal is, however, continuously influenced by the cardioaccelerating activities of the sympathetic system and the cardioinhibitory activities of the parasympathetic system. 11-13

In the chick embryo, the HR increases from 50 bpm at about 1.5 days to 220 bpm at 8 days. 14, 15 This increase takes place independently of the development of the neural control.

In mammalian species, including man and sheep, the heart begins its rhythmic beating 21 to 23 days after conception and before innervation is developed. 14-19 In the sheep, the fetal HR ranges between 160 and 180 bpm during most of the gestational period. However, anatomic and functional evidence of cardiac innerva450 Zugaib et.al.

October 15, 1980

Am. J. Obstet. Gynecol.

tion exists only at about 70 to 80 days of gestation. 7, 12–19 At this period, the parasympathetic tone of the resting HR is minor, while the sympathetic tone is somewhat greater. 7 At near-term pregnancy, the tones exerted by the two divisions are nearly equal. After birth, a striking surge in the parasympathetic tone takes place while the sympathetic tone remains at the levels existing in the fetus. 7

These same studies have shown that during the neonatal period, a progressive and weekly decrease in the resting HR occurs throughout the neonatal period and persists until the adult rate is reached. These postnatal changes were shown to be independent of the activities of the parasympathetic and sympathetic systems. It is believed that they are related to modifications in the action potential of the conducting systems of the heart.<sup>7</sup>

The present data, obtained from unanesthetized lambs studied from the first week to the eighth week of postnatal life, are in general agreement with those previously reported. The pattern of the weekly decrease in the resting HR of the newborn lamb observed in this series is not significantly different from that reported by others. Likewise, the marked surge in the parasympathetic tone of the resting HR (reflected by the magnitude of the response to atropine), as contrasted with the lesser sympathetic tone during the first few weeks of the neonatal period, is clearly evident.

The behavior of the newborn HR after pharmacologic cardiac denervation (simultaneous cholinergic and beta-adrenergic blockade) is very similar to that of the adult animal given the same drugs or to the adult heart subjected to surgical denervation. 11–13, 20 It provides evidence that, in the resting state and under normal circumstances, the HR is under strong inhibitory influences; when these influences are blocked, the heart rate tends to accelerate.

HR variability. Spontaneous variations in the resting HR have probably been observed ever since man learned how to feel his pulse. Circadian changes in the HR and other circulatory parameters of the adult animal have been described by numerous authors. <sup>11–13</sup> Since these changes have not been of any physiologic consequences, investigators have not attributed to them any significant role in the maintenance of circulatory homeostasis.

In recent years, instantaneous variations in HR have been observed in in vitro studies of the automaticity of the conducting system of the adult heart.<sup>21, 22</sup> These variations have been attributed to resonances of electric impulses generated in the heart. More recently, periodic variations in the mean HR, arterial pressure, cardiac output, and systemic resistance were observed in

chronically instrumented dogs studied over a period of 8 to 10 hours.<sup>23</sup> These variations have been attributed to adjustments of the cardiovascular system to periodic changes in metabolic demands of the living organism.

In the present studies, we attempted to shed light on the mechanisms of beat-to-beat variability in the HR in an experimental model in which many artifacts and interfering variables were eliminated. Although we used a somewhat different approach in calculating the HR variability, the results should be applicable since they were obtained by a methodology that proved efficient in detecting minor changes in either amplitude or frequency of cardiac cycles by computer simulation.

The present data show that, while the resting HR was decreasing weekly throughout the period of neonatal growth, the long- and short-term variabilities did not change significantly. This seems to suggest that the progressive long-term modifications in the intrinsic mechanisms that are responsible for the weekly decrease in the newborn resting HR may not have an important role in the genesis of beat-to-beat-variabilities.

This assumption appears to contradict the results obtained with acute pharmacologic denervation of the heart which showed a consistent and marked diminution of both the long-term and short-term variabilities. On theoretical grounds, pharmacologic denervation should abolish neural control of the HR and should leave the heart beating at a rate set by its own intrinsic mechanisms. This contradiction, however, is more apparent than real. Acute pharmacologic denervation releases the heart from neural inhibition and results in transient tachycardia. This mechanism is entirely different from the slowly occurring alterations in the action potential that are responsible for the progressive decrease in HR during the neonatal period.

Nevertheless, the fact that simultaneous inhibition of the influences of the two divisions of the autonomic nervous system on HR markedly decreased the beatto-beat variabilities suggests that the integrity of the autonomic nervous system, including its central control, may be a major contributor to the appearance of this phenomenon.

This hypothesis receives support from information available in the literature, as well as from the results of the present studies. It has been shown that HR variabilities disappear in comatose conditions and diminish during sleep. <sup>1-6</sup> In both situations, central and autonomic nervous activities are depressed. Our data show that cholinergic blockade with atropine, which increased the resting HR, inhibited both the long- and short-term variabilities. Such an inhibition appeared to

be greater during the first 3 postnatal weeks when the surge in the parasympathetic control of the resting HR was at its peak.

On the other hand, beta-adrenergic blockade, which elicited bradycardia, likewise decreased both the longand short-term variabilities. However, the pattern of the decrease from week to week differed entirely from that observed after cholinergic blockade. The problem is further complicated by the fact that when tachycardia of about the same magnitude as that produced by atropine was elicited by adrenergic stimulation with isoproterenol, long-term variability increased while short-term variability did not change significantly. From all of these results, one may be able to conclude that: (1) a change in the resting HR per se may not affect beat-to-beat variability; (2) the beta-adrenergic and cholinergic systems play an important role in the genesis of the beat-to-beat variability of the HR; (3) the role of the autonomic nervous system in beat-to-beat variability seems to be independent of its net effect on the resting HR; whether the net effect of inhibiting the autonomic nervous system is bradycardia (as occurs after propranolol) or tachycardia (after atropine), the end result is an inhibition of beat-to-beat variability; and (4) the influence of the parasympathetic limb on short- and long-term beat-to-beat variability seems to be at its peak in the early period of neonatal life, whereas that of the beta-adrenergic system reaches a maximum at a later period. The reasons for these differences, as well as the exact mechanisms by which the two limbs of the autonomic nervous system produce these patterns of HR variabilities, have not been determined.

Another aspect of this problem which deserves an additional comment is related to the relationship between beat-to-beat variability and the health condition of the animal, be it fetus or neonate.

In attempting to discuss this question, one should ask what are the hemodynamic consequences of alterations. in the beat-to-beat variability. It is claimed on a purely clinical basis that disappearance of beat-to-beat variability of the heart rate is ominous to the fetus, 1-6 but no one has been able to explain what circulatory events characterize this ominous condition.

The present studies, performed on healthy, unanesthetized lambs, show that the arterial pressure and blood gases did not change significantly during periods of pharmacologic manipulation in which the beat-tobeat variabilities and the HR itself were markedly altered. Although we did not monitor the status of the cardiac output in these experiments, it is doubtful that this circulatory parameter did change to any significant degree during the periods of variability since the arterial pressure remained stable. Furthermore, it has been repeatedly shown that transient changes in the HR itself, let alone its beat-to-beat variability, may be compensated for by an increase in the stroke volume so that the cardiac output may remain unchanged.

Thus, while it may be of some interest for clinicians to continue accumulating data on beat-to-beat variabilities of the fetal heart, a great deal of caution should be used in relying on its pathophysiologic significance. It is obvious that more research is needed to elucidate the various complex mechanisms that generate beat-to-beat variability of the HR as well as the hemodynamic basis of this phenomenon.

# REFERENCES

1. Nochimson, D. J., Turbeville, J. S., Terry, J. E., et al.: The nonstress test, Obstet. Gynecol. 51:419, 1978.

De Haan, J., Bemmel, J., Versteeg, B., Veth, A., Stolte, L., Janssens, J., and Eskes, T.: Quantitative evaluation of fetal heart rate patterns, Eur. J. Obstet. Gynaecol. Biol. Reprod. 3:95, 1971.

3. Trierweiler, M., Freeman, R., and James, J.: Baseline fetal heart rate characteristics as an indicator of fetal status during the antepartum period, Am. J. OBSTET. GYNECOL. 125:618, 1976.

4. Dalton, K. J., Dawes, G. S., and Patrick, J. E.: Diurnal, respiratory, and other rhythms of fetal heart rate in lambs, Am. J. Obstet. Gynecol. 127:414, 1977

5. Organ, L. W., Hawrylyshyn, P. A., Goodwin, J. W., Quilligan, J. E., and Bernstein, A.: Quantitative indices of short- and long-term heart rate variability, Am. J. OBSTET. Gynecol. 130:20, 1978.

Modanlou, H. D., Freeman, R. K., and Braly, P.: A simple method of fetal and neonatal heart rate beat-to-beat variability quantitation: Preliminary report, Am. J. Obstet. GYNECOL. 127:861, 1977

7. Woods, J. R., Jr., Dandavino, A., Murayama, K., Brink-

man, C. R., III, and Assali, N. S.: Autonomic control of cardiovascular functions during neonatal development and in adult sheep, Circ. Res. 40:401, 1977

8. Assali, N. S., Brinkman, C. R., III, and Nuwayhid, B.: Comparison of maternal and fetal cardiovascular functions in acute and chronic experiments in the sheep, Am. J. OBSTET. GYNECOL. 120:411, 1974.

9. Yeh, S. Y., Forsythe, A., and Hon, E. H.: Quantification of fetal heart beat-to-beat interval differences, Obstet. Gynecol. 41:355, 1973.

10. Brown, M. B., and Forsythe, A. B.: Robust tests for the quality of variances, J. Am. Stat. Assoc. 69:364, 1974.

11. Braunwald, E.: Regulation of circulation, N. Engl. J. Med. 290:1420, 1974.

12. Glick, G., and Braunwald, E.: Relative roles of the sympathetic and parasympathetic nervous systems in the reflex control of heart rate, Circ. Res. 16:363, 1965

13. Higgins, C. B., Vatner, S. F., and Braunwald, E.: Parasympathetic control of the heart, Pharmacol. Rev.

14. Adolph, E. F.: Ranges of heart rates and their regulation at various ages (rat), Am. J. Physiol. 212:595, 1967.

- 15. Walker, D.: Functional development of the autonomic innervation of the human fetal heart, Biol. Neonate 25:31, 1975.
- Vappaavouri, E. K., Shinebourne, E. A., Williams, R. L., Heymann, M. A., and Rudolph, A. M.: Development of cardiovascular responses to autonomic blockade in intact fetal and neonatal lambs, Biol. Neonate 22:177, 1973.
- 17. Lebowitz, E. A., Novick, J. S., and Rudolph, A. M.: Development of myocardial sympathetic innervation in the fetal lamb, Pediatr. Res. 6:887, 1972.
- Friedman, W. F., Pool, P. E., Jacobowitz, D., Seagren, S. C., and Braunwald, E.: Sympathetic innervation of the developing rabbit heart—biochemical and histochemical comparisons of fetal, neonatal and adult myocardium, Circ. Res. 23:25, 1968.
- Dawes, G. S.: Fetal and Neonatal Physiology, 1968, Chicago, Year Book Medical Publishers, Inc.
- 20. Warner, H. R., and Russell, R. O., Jr.: Effects of combined sympathetic and vagal stimulation on heart rate in the dog, Circ. Res. 24:567, 1969.
- 21. Saito, T., Otoguro, M., and Matsubara, T.: Electrophysiological studies on the mechanism of electrically induced sustained rhythmic activity in the rabbit right atrium, Circ. Res. 42:199, 1978.
- 22. Ablessie, M. A., Bonke, F. I. M., and Schopman, F. J. G.: Circus movement in rabbit atrial muscle as a mechanism of tachycardia, Circ. Res. **41**:9, 1977.
- Anderson, D., Yingling, J., and Sagawa, K.: Minute-tominute covariations in cardiovascular activity of conscious dogs, Am. J. Physiol. 236:H434, 1979.

# Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978. Therefore, all manuscripts must be accompanied by the following written statement, signed by one author: "The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C. V. Mosby Company in the event the work is published. The undersigned author warrants that the article is original, is not under consideration by another journal, and has not been previously published. I sign for and accept responsibility for releasing this material on behalf of any and all co-authors." Authors will be consulted, when possible, regarding republication of their material.

# Mechanisms of beat-to-beat variability in the heart rate of the neonatal lamb

# II. Effects of hypoxia

MARCELO ZUGAIB\*
ALAN B. FORSYTHE
BAHIJ NUWAYHID\*\*
STEPHEN M. LIEB
KHALIL TABSH
RISTO ERKKOLA\*\*\*
ETSUO USHIODA\*\*\*
S. MURAD
C. R. BRINKMAN III
N. S. ASSALI
Los Angeles, California

The effects of acute hypoxia on the resting arterial pressure as well as on heart rate and its beat-to-beat variability were studied in chronically instrumented, unanesthetized newborn lambs at 2 to 8 weeks of neonatal life. Lung ventilation with a gas mixture containing 10% oxygen and 3% carbon dioxide decreased arterial blood Po<sub>2</sub> by about 50% in all animals regardless of age without significantly altering blood pH and PCo<sub>2</sub>. This degree of hypoxia produced a mild pressor response, accompanied by a significant tachycardia; the pattern of these changes, however, differed somewhat according to neonatal growth. The impact of hypoxia on beat-to-beat variability of the neonatal heart rate also varied with age. When the lambs were 2 to 3 weeks old, both the long- and short-term variabilities decreased progressively during hypoxia and the decrement reached a maximum at 10 minutes of oxygen deprivation. As the lambs became older, however, there was some initial and transient increase in the long- and short-term variabilities in the early period of hypoxia but thereafter the changes were inconsistent. The significance of these observations is discussed in terms of our knowledge of the pathophysiologic alterations in the cardiovascular system produced by acute hypoxia. (Am. J. Obstet. Gynecol. 138:453, 1980.)

IN A PREVIOUS REPORT, we presented data bearing on the contributions of the two divisions of the au-

From the Departments of Obstetrics and Gynecology and Biomathematics, University of California, Los Angeles School of Medicine.

Supported by Grants HL 01755 and HL 13634 from the National Institutes of Health.

Received for publication October 30, 1979.

Revised June 23, 1980.

Accepted June 30, 1980.

Reprint requests: Bahij Nuwayhid, M.D., University of California, Los Angeles School of Medicine, Department Obstetrics and Gynecology, Los Angeles, California 90024.

tonomic nervous system and of the intrinsic mechanisms of heart rate control to the genesis of beat-to-beat variability in the heart rate of the neonatal lamb. The data suggested that the activities of the sympathetic and parasympathetic nervous system contribute significantly to the appearance of beat-to-beat variability.

Hypoxia during the perinatal period has been impli-

\*Fellow in Reproductive Physiology, sponsored in part by "Conselho Nacional de Desenvolvimento Científico e Tecnologico," Brazil.

\*\*Recipient of Research Career Development Award HD 00253.

\*\*\*National Institutes of Health Fogarty Fellow in Reproductive Physiology.

	Control				
		2½ min	5 min	10 min	Recovery
рН	$7.45 \pm 0.02$	$7.47 \pm 0.02$	$7.47 \pm 0.03$	$7.47 \pm 0.02$	$7.46 \pm 0.02$
Pco <sub>2</sub> (mm Hg)	$33 \pm 2$	$31 \pm 2$	$31 \pm 2$	$32 \pm 2$	$32 \pm 2$
Po <sub>2</sub> (mm Hg)	$82 \pm 5$	$45 \pm 3$	$43 \pm 3$	$42 \pm 3$	$83 \pm 7$

**Table I.** Mean values (±1 SE) for arterial blood gases and pH during the periods of study

cated as a major cause of alterations in the beat-to-beat variability of the heart rate.<sup>2, 3</sup> The mechanisms by which hypoxia produces such alterations, however, have not been adequately assessed.

The present report deals with the effects of experimentally induced hypoxia on the beat-to-beat variability of the heart rate of the neonatal lamb. The reasons for the selection of the newborn lamb as the experimental model have already been outlined.<sup>1</sup>

# Material and methods

Near-term ewes of mixed breed with dated singleton gestations were allowed to deliver spontaneously in our animal facilities; hence the exact age of each lamb was known. The lambs were housed with their mothers so that normal lactation could be accomplished until they were able to eat the same diet given to the ewes and drink on their own during the period of observation.

Each lamb was allowed a 3-4 day period of neonatal adjustment before it was subjected to surgery. Chronic instrumentation of the lamb was accomplished under aseptic conditions by the same techniques reported previously.<sup>1, 4</sup>

A postoperative recovery period of at least 4 days was allowed before the studies were begun. The lamb's activities, feeding habits, respirations, muscle tone, and weight were checked daily while hemoglobin, hematocrit, blood respiratory gases, and pH were analyzed at frequent intervals.

A total of 44 experiments (N) with hypoxia were carried out on seven newborn lambs at different periods of neonatal growth. No more than three experiments were done on a given animal each week, and the same lamb was observed for 3 to 8 weeks during the neonatal period. To simplify the presentation of the results, the animals were grouped by age as follows: Group 1 (N = 13) represents the 2 to 3-week-old lambs; Group 2 (N = 13) represents the 4 to 5-week-old lambs; and Group 3 (N = 18) represents the 6 to 8-week-old lambs.

Hypoxia was induced by allowing the lamb to breathe a gas mixture consisting of 10% oxygen and 3% carbon dioxide in nitrogen for 10 minutes. An open system was utilized with the gas mixture flowing into a bag fitted around the head of the animal.

The experimental protocol was as follows: (1) A control period lasted 30 to 40 minutes, during which the animal stood quietly in its cage while heart rate, beatto-beat variability, and arterial pressure were recorded every 3 to 5 minutes; blood gas and pH values were determined three times. The averages of all these readings were taken as the control values for that animal on that day. (2) A testing period then followed, during which the gas mixture was administered at a constant rate for 10 minutes. The circulatory parameters were recorded continuously while blood gas and pH levels were determined at 2.5, 5, and 10 minutes. (3) A recovery period lasting 10 minutes ended the experiment; during this period, the lamb was allowed to breathe room air while the recording of the circulatory parameters was made continuously and blood gas values were determined once or twice.

Blood pressure, blood respiratory gases, pH, hemoglobin, and hematocrit were measured by techniques in current use in our laboratories. Resting heart rate and long-term and short-term variabilities were computed as previously described. The response to hypoxia was determined at 2½, 5, and 10 minutes; the maximum changes observed at each time were related to the control values observed on that day.

For statistical treatment of the data, each animal was used as its own control, and the results were submitted to a multiple regression analysis to account for the differences between animals and ages, as previously described. Probability values were calculated by repeated measures of analysis of variance and by multiple regression.

# Results

Conditions of the animals. All lambs had recovered from operation and had resumed their normal activities and feeding habits prior to the initiation of the experiments. The control values for the various circulatory parameters and blood respiratory gases were within the range of the data previously published.<sup>1, 4</sup>

# Effects of hypoxia.

Blood respiratory gases and pH. In Table I are listed the average values for all animals for blood Po<sub>2</sub>, PCo<sub>2</sub>, and pH observed during the control period, at 2½, 5, and 10 minutes of hypoxia, and during recovery. Blood pH

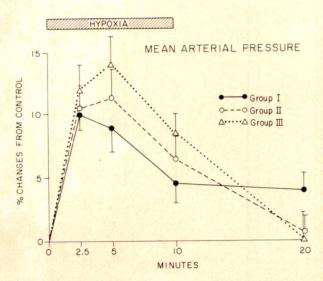


Fig. 1. Changes in the mean systemic arterial pressure observed during hypoxia and in the recovery period in the three groups of animals. Note the similar and moderate rise in the arterial pressure observed during the early period of hypoxia in the three groups. Note also the dissimilar behavior at 5 minutes (values are mean  $\pm$  1 SE).

and PCo<sub>2</sub> did not change significantly throughout the periods of study. Mean control values for the three groups of lambs for arterial blood Po<sub>2</sub> averaged 82 ± 5 mm Hg; it decreased to a mean of 45 mm Hg at 2½ minutes, 43 mm Hg at 5 minutes, and 42 mm Hg at 10 minutes of hypoxia. During the recovery period while the lamb was breathing room air, blood Po<sub>2</sub> returned to an average of 83 mm Hg. There was no significant difference between blood Po<sub>2</sub> values of the three groups of animals at any time during the study.

Arterial pressure. In Fig. 1 are presented the changes from control in the mean systemic arterial pressure observed during the hypoxic and recovery periods in the three different groups of lambs. After  $2\frac{1}{2}$  minutes of hypoxia, the arterial pressure increased by 10% to 13% (P < 0.001). Although the increase seemed to be less in the younger lambs, the difference between the three groups was not significant.

After 5 minutes of hypoxia, the mean arterial pressure of the younger lambs (Group 1) decreased somewhat from the level reached after  $2\frac{1}{2}$  minutes while the pressure of the lambs in Groups 2 and 3 either remained at the level reached at  $2\frac{1}{2}$  minutes or rose further (Fig. 1). The difference from control was highly significant for the three groups (P < 0.01), but when the mean arterial pressure changes observed at 5 minutes of hypoxia are compared for the three groups, only the difference between Groups 1 and 3 was significant (P < 0.01) (Fig. 1).

At 10 minutes of the hypoxic period, the mean arte-

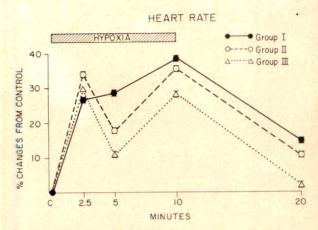


Fig. 2. Changes in the heart rate observed during hypoxia and in the recovery period in the three groups of lambs. Note the fall in heart rate in Groups 2 and 3 as contrasted with Group 1. Note also the "escape" of heart rate in the older lambs (values are mean  $\pm$  1 SE).

rial pressure decreased significantly from the levels previously reached in all three groups of animals (Fig. 1).

During the recovery period, the arterial pressure returned toward control values (Fig. 1).

Resting heart rate. In Fig. 2 are presented the average changes from control in the resting heart rate at different times during hypoxia and during the recovery period. The heart rate of the three groups of lambs increased by about 30% (P < 0.001) after 2½ minutes of hypoxia. The difference between the increment among the three groups was not significant. After 5 minutes of hypoxia, the average heart rate of Group 1 (2 to 3-week-old lambs) remained at about the levels recorded at 21/2 minutes; however, the heart rate of Groups 2 and 3 decreased significantly from the levels previously reached (Fig. 2). The difference between the mean changes in heart rate of Group 1 and of Groups 2 and 3 at 5 minutes was statistically significant (P < 0.01). After 10 minutes of hypoxia, the mean heart rate of Group 1 increased further to about 40% from control while the heart rate of Groups 2 and 3 rose again to about that level after it had decreased (Fig. 2); the difference between the heart rate responses of the three groups at 10 minutes of hypoxia was not statistically significant.

During the recovery period the heart rate of all of the three groups of lambs decreased significantly (P < 0.01) from the levels it had reached at the peak of hypoxia (Fig. 2).

Long-term and short-term variabilities. In Fig. 3 are presented the changes in long-term variability observed during the hypoxic and recovery periods. In the younger lambs (Group 1), hypoxia decreased long-term



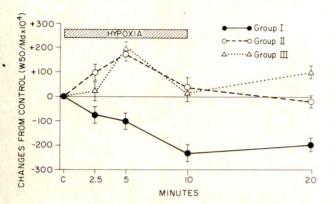


Fig. 3. Changes in long-term variability observed during hypoxia and in the recovery period in the three groups of lambs. Note the progressive decrease in long-term variability of the younger animals as contrasted with the transient increase of the older lambs (values are mean  $\pm 1$  SE).

variability progressively and the decrement reached significantly low values at 10 minutes of the hypoxic period; long-term variability remained at that depressed level even after 10 minutes of recovery when the animals were breathing room air (Fig. 3).

In Groups 2 and 3, however, hypoxia produced a different pattern of changes in the long-term variability. There was an increase which reached a peak after 5 minutes of hypoxia (P < 0.01); thereafter, long-term variability returned toward control values (Fig. 3).

In Fig. 4 are presented the changes in the short-term variability observed in the three groups of animals. In Group 1 short-term variability decreased progressively and significantly during hypoxia; the lowest values were observed at 10 minutes of hypoxia. During the recovery period, short-term variability returned toward control values (Fig. 4).

In Group 2, short-term variability did not change consistently during hypoxia; but in Group 3, it tended to increase during the early period of hypoxia. During the recovery period, short-term variability increased significantly in Groups 2 and 3.

### Comment

Cardiovascular effects of hypoxia. If one attempts to synthesize the enormous and conflicting literature on the cardiovascular response to oxygen deprivation, one is led to conclude that the impact of hypoxia on the circulation depends on: (1) animal species and age, (2) experimental conditions including anesthesia, (3) methodology of inducing oxygen curtailment and of monitoring its effects on the various cardiovascular

# SHORT TERM VARIABILITY (W50 Di)

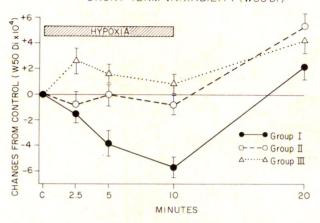


Fig. 4. Changes in short-term variability observed during hypoxia and in the recovery period in the three groups of lambs. Note the different behavior of Group 1 as contrasted with the older animals (values are mean  $\pm$  1 SE).

functions, and (4) the degree and duration of hypoxia, together with the presence or absence of acidosis.

In the adult man, dog, and sheep, lung ventilation with a gas mixture containing 7% to 8% oxygen results in moderately severe hypoxia with the arterial Po<sub>2</sub> falling to 30 to 40 mm Hg. This degree of hypoxia elicits a moderate rise in the arterial pressure (10% to 15%) and a significant tachycardia (40%) within the first 2 to 3 minutes. The cardiac output may increase and the regional circulation may respond differently, depending on the vascular bed under study. Some anesthetic agents may alter this pattern of response.<sup>5–8</sup>

In the rabbit, which has been the experimental model of choice for the study of many aspects of hypoxia, the circulatory response resembles that described above. It differs, however, if the hypoxia becomes extremely severe.<sup>5</sup>

The studies of Downing<sup>8</sup> in the newborn lamb have shown that a fall in blood Po<sub>2</sub> from 82 to 26 mm Hg with the pH remaining normal leads to a significant increase in heart rate and systemic blood flow. The myocardial functions may be affected adversely, particularly in the presence of acidosis. This author did not differentiate the response according to the age of the newborn lamb.

In the fetal lamb, the literature is almost unanimous in indicating that hypoxia induced by ventilating the maternal lung with 6% oxygen results in fetal brady-cardia and a slight or no rise in the arterial pressure. 9, 10 Various hypotheses have been advanced to explain the mechanisms of the fall in heart rate of the fetus during hypoxia as opposed to the rise in the adult. Some au-

thors<sup>11</sup> believe that during fetal life the adrenergic system is almost totally saturated by the requirement to maintain a heartbeat at a relatively fast rate. Consequently, most stressful stimuli would more rapidly activate the parasympathetic system and elicit bradycardia. The possibility that the decrease in the fetal heart rate during hypoxia might be related to myocardial depression has also been raised. 10

The mechanisms by which hypoxia affects the various cardiovascular functions have been controversial.

The studies of Korner and Edwards, 5-7 in the adult rabbit, have outlined the afferent, central, and efferent neural pathways for the action of acute hypoxia. These studies suggest that inputs for the hypoxic stimuli arise from arterial chemoreceptors, baroreceptors, and lung inflation receptors. The stimuli are then relayed to specific areas in the central nervous system. The efferent pathways comprise the two limbs of the autonomic nervous system, as well as the adrenal medulla. Downing8 believes that this latter organ plays an important role in the cardiovascular response to hypoxia in the newborn lamb.

The studies of Korner<sup>5</sup> seem to indicate that the increase in the adult heart rate elicited by hypoxia is related not only to stimulation of the beta-adrenergic system but also to a marked inhibition of vagal effects. In fact, the vagal inhibition which precedes the adrenergic stimulation may reach about 90% of its control activities if the hypoxia becomes severe.

The increase in cardiac output that follows oxygen deprivation is thought to be compensatory in nature and is probably related to the increase in both the heart rate and stroke volume. The arterial pressure rise is believed to be related to a moderate rise in the systemic vascular resistance which, in turn, represents the net effect of hypoxia on the various regional resistances.<sup>5-8</sup>

Recently Senges and co-workers<sup>12</sup> performed in vitro studies in which they described another action of hypoxia on the adult heart. Using intracellular microelectrodes, these authors observed that hypoxia decreased the rate of spontaneous impulse initiation in the sinoatrial nodal fibers. They also observed a decrease in the amplitude of action potentials of the sinoatrial and atrioventricular nodes. These authors concluded that acute hypoxia interferes with the overall activities of the pacemaker centers and conducting systems of the heart.

The present data obtained from unanesthetized newborn lambs studied at different periods of neonatal development show that the cardiovascular response to hypoxia differs somewhat according to age, even when the degree of oxygen deprivation is the same.

The magnitude of the rise in the arterial pressure and heart rate in response to the same hypoxic level reached after the first 2 to 3 minutes was similar in the three groups of animals. In the younger group (2 to 3 weeks), however, the heart rate rose further at 5 minutes of hypoxia; in contrast, in the two older groups (Groups 2 and 3) the heart rate decreases significantly from the levels reached earlier, even though the blood Po<sub>2</sub> values during that period were the same in all three groups. This different behavior in heart rate in relation to age seems to suggest a different degree of baroreceptor activities in response to the initial rise in pressure. It is possible that at 2 to 3 weeks of neonatal development, the baroreceptors are not as mature as those of later age and, consequently, they do not possess the ability to respond adequately to an arterial pressure increase.

At 10 minutes of hypoxia, the heart rate of the two older groups of lambs seems to have escaped from the baroreceptor influences since it rose again to the previous levels seen during the early period of hypoxia. These findings suggest that after the initial baroreceptor stimulation brought about by the pressure increase, hypoxia further stimulated the adrenergic system and this overstimulation overcame the baroreceptor activities. Consequently, the heart rate rebounded to the previously reached higher levels. Such patterns of response appear to agree with the concept of sympathetic-parasympathetic interactions in cardiovascular behavior during progressive oxygen deficiency.

Beat-to-beat variability. Although it is somewhat difficult to explain precisely the mechanisms of the changes in the beat-to-beat variability observed during hypoxia in these three groups of neonatal lambs, some hypothesis could be advanced.

From our previous studies, we concluded that: (1) some degree of autonomic activity is necessary for the genesis of beat-to-beat variability and (2) during the early period of neonatal development (2 to 3 weeks), the parasympathetic influences are much greater than the sympathetic influences on both long-term and short-term variability. As the newborn lamb becomes older, the sympathetic influence on beat-to-beat variability becomes more dominant.1

The behavior of the long-term and short-term beatto-beat variability of the newborn lamb of 2 to 3 weeks of age during hypoxia resembles the pattern observed after parasympathetic blockade with atropine during that period of neonatal development. This suggests that hypoxia, in addition to its adrenergic-stimulating activities, inhibits vagal activities at a time of development when these latter are at their peak. This assumption is in general agreement with the concept of hypoxic vagal inhibition as advanced by Korner.5

The contrasting patterns of changes in beat-to-beat variability observed in the two older groups of lambs are also consistent with the data obtained from lambs of similar age after sympathetic and parasympathetic blockades and after beta-adrenergic stimulation. In these two older groups of lambs, the effects of hypoxia on beat-to-beat variability resemble more closely those observed after beta-adrenergic stimulation.1 These findings point out the complexity of the neurohumoral regulatory mechanisms of heart rate control and how these mechanisms change with the growth of the

It is difficult to extrapolate from the present findings obtained from newborn lambs subjected to a wellcontrolled acute hypoxia to those which might occur during intrauterine life, particularly in human subjects.

When distressful situation in the fetus is clinically diagnosed, it is usually placed under the general "um-

brella" of fetal hypoxia. It is, however, well known that this so-called fetal hypoxia is not a well-defined, pathophysiologic entity comparable to that produced experimentally in animals. Clinically, fetal hypoxia resulting from episodes such as cord compression is related not only to oxygen deficit but also to a decrease in the filling of the heart and in the placental excretion of catabolic products. Its net effects on the cardiovascular system may be totally different from those produced in the newborn or adult animal by inhalation of a gas mixture poor in oxygen.

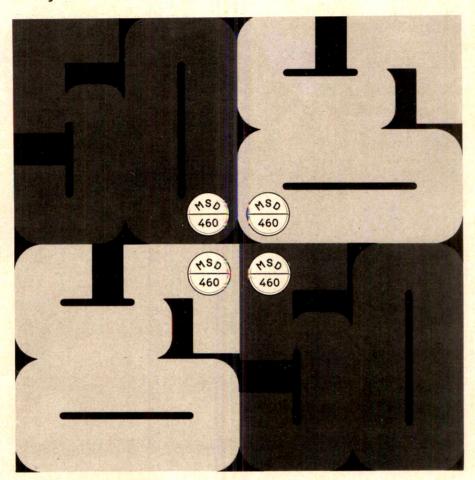
Nevertheless, the fact that the literature seems to agree that hypoxia decreases both long-term and short-term variability of the human fetal heart rate suggests that the mechanisms may be similar to those observed in the early newborn lambs. This suggestion does not rule out, however, other effects of hypoxia on the myocardium and its pacemaking and conducting mechanisms.

# REFERENCES

- 1. Zugaib, M., Forsythe, A. B., Nuwayhid, B., Lieb, S. M., Tabsh, K., Erkkola, R., Ushioda, E., Brinkman, C. R., III, and Assali, N. S.: Mechanisms of beat-to-beat variability in the heart rate of the neonatal lamb. I. Influence of the autonomic nervous system, Am. J. Obstet. Gynecol. 138:444, 1980.
- 2. De Haan, J., Bemmel, J., Versteeg, B., Veth, A., Stolte, L., Janssens, J., and Eskes, T.: Quantitative evaluation of fetal heart rate patterns, Eur. J. Obstet. Gynecol. 3:95, 1971.
- 3. Trierweiler, M., Freeman, R., and James, J.: Baseline fetal heart rate characteristics as an indicator of fetal status during the antepartum period, Am. J. OBSTET. GYNECOL. 125:618, 1976.
- 4. Woods, J. R., Jr., Dandavino, A., Murayama, K., Brinkman, C. R., III, and Assali, N. S.: Autonomic control of cardiovascular functions during neonatal development and in adult sheep, Circ. Res. 40:401, 1977
- 5. Korner, P. I.: Integrative neural cardiovascular control, Physiol. Rev. 51:312, 1971.
- 6. Korner, P. I.: Control of the systemic circulation in hypoxia, in Proceedings of the Twenty-third International Congress of Physiology, Tokyo, 1965. Amsterdam,

- 1965, Excerpta Medica, International Congress Series
- No. 87, pp. 137-152.
  7. Korner, P. I., and Edwards, A. W. T.: The immediate effects of acute hypoxia on the heart rate, arterial pressure, cardiac output and ventilation of the unanesthetized
- rabbit, Q. J. Exp. Physiol. **45:**113, 1960. 8. Downing, S. E.: Neural regulation of circulation during hypoxia and acidosis with special reference to the newborn, Fed. Proc. 31:1209, 1972.
- 9. Millard, R. W., Baig, H., and Vatner, S. T.: Prostaglandin control of the renal circulation in response to hypoxemia in the fetal lamb in utero, Circ. Res. 45:172, 1979.
- 10. Dilts, P. V., Jr., Brinkman, C. R., III, Kirschbaum, T. H., and Assali, N. S.: Uterine and systemic hemodynamic interrelationships and their response to hypoxia, Am. J. OBSTET. GYNECOL. 103:138, 1969.
- 11. Assali, N. S., Bekey, G. A., and Morrison, L. W.: Fetal and neonatal circulation, in Assali, N. S., editor: Biology of Gestation, New York, 1968, vol. 2, Academic Press, Inc.,
- 12. Senges, J., Brachmann, J., and Pelzer, D.: Effect of hypoxia on the sinoatrial node, atrium and atrioventricular node in the rabbit heart, Circ. Res. 44:856, 1979.

for neurogenic atony of the urinary bladder with retention, higher titrated dosages may be needed (up to 200 mg/day)



# **MSD** announces

# ECHOLINE

(BETHANECHOL CHLORIDE | MSD)

when higher titrated dosages are indicated

After titration, dosages as high as 50 mg t.i.d. or q.i.d. have been effectively employed in neurogenic atony of the urinary bladder as well as for the treatment of postoperative and postpartum nonobstructive (functional) urinary retention.

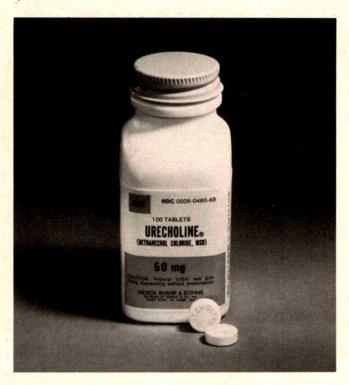
- Helps to initiate micturition and empty the bladder.
- Helps to reduce the frequency of bladder catheterization Contraindicated in hypersensitivity to

URECHOLINE, hyperthyroidism, pregnancy, peptic ulcer, latent or active bronchial asthma, pronounced bradycardia or hypotension, vasomotor instability, coronary artery disease, epilepsy, and parkinsonism.

URECHOLINE should not be used when the strength or integrity of the gastrointestinal or bladder wall is in question or in the presence of mechanical obstruction. If necessary, the effects of the drug can be abolished promptly by atropine.

for neurogenic atony of the urinary bladder with retention, higher titrated dosages may be needed (up to 200 mg/day)

# JEW 50-mg LABLETS URECHOLINE® (BETHANECHOL CHLORIDE | MSD)



Contraindications: Hypersensitivity to Tablets URECHOLINE (Bethanechol Chloride, MSD) or to any component of Injection URECHOLINE; hyperthyroidism, pregnancy, peptic ulcer, latent or active bronchial asthmá, pronounced bradycardia or hypotension, vasomotor instability, coronary artery disease, epilepsy, and parkinsonism. Should not be employed when the strength or integrity of the gastrointestinal or bladder wall is in question, or in the presence of mechanical obstruction; when increased muscular activity of the gastrointestinal tract or urinary bladder might prove harmful, as following recent urinary bladder surgery, gastrointestinal resection and anastomosis, or when there is possible gastrointestinal obstruction; in bladder neck obstruction, spastic gastrointestinal disturbances, acute inflammatory lesions of the gastrointestinal tract, or peritonitis; or in marked vagotonia.

Warnings: The sterile solution is for subcutaneous use only. It should never be given intramuscularly or intravenously. Violent symptoms of cholinergic overstimulation, such as circulatory collapse, fall in blood pressure, abdominal cramps, bloody diarrhea, shock, or sudden cardiac arrest are likely to occur if the drug is given by either of these routes. Although rare, these same symptoms have occurred after subcutaneous injection, and may occur in cases of hypersensitivity or overdosage.

**Precautions:** Special care is required in patients receiving ganglion blocking compounds because a critical fall in blood pressure may occur; usually, severe abdominal symptoms appear before there is such a fall in blood pressure. In urinary retention, if the sphincter fails to relax as the drug contracts the

bladder, urine may be forced up the ureter into the kidney pelvis; if there is bacteriuria, this may cause reflux infection.

Adverse Reactions: Abdominal discomfort, salivation, flushing of the skin ("hot feeling"), sweating. Large doses more commonly result in effects of parasympathetic stimulation, such as malaise, headache, sensation of heat about the face, flushing, colicky pain, diarrhea, nausea and belching, abdominal cramps, borborygmi, asthmatic attacks, and fall in blood pressure.

Atropine is a specific antidote. The recommended dose for adults is 0.6 mg (1/100 grain). The recommended dosage in infants and children up to 12 years of age is 0.01 mg/kg repeated every two hours as needed until the desired effect is obtained, or adverse effects of atropine preclude further usage. The maximum single dose should not exceed 0.4 mg. Subcutaneous injection of atropine is preferred except in emergencies when the intravenous route may be employed. When Injection URECHOLINE is used, a syringe of atropine sulfate should always be available.

How Supplied: Tablets, containing 5 mg, 10 mg, 25 mg, or 50 mg bethanechol chloride each, in bottles of 100 and single-unit packages of 100; Injection, 5 mg per ml, is a clear, colorless solution, and is supplied in boxes of 6 × 1-ml vials.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, PA 19486

# INDEX TO ADVERTISERS

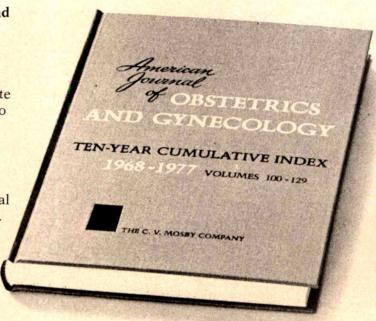
Capital Area Community Health Plan Opportunity Available 20	Opportunities Available 10, 26
College of Medicine and Dentistry of New Jersey Opportunity Available 20	Norwich-Eaton Pharmaceuticals  Macrodantin 22, 23, 24
Hitchcock Clinic Opportunity Available 31	O.T.E. Biomedica  Cardiotocograph 32
Hoffman-La Roche Inc.  Gantanol12, 13, 14	Parke-Davis Division of Warner-Lambert Company           Estrovis
Hospital Corporation of America Opportunity Available 8	Purdue Frederick Company, The  Betadine 30, 31
Jobst Institute, Inc.  VIP Pregnancy Support 25	Searle Laboratories  CU-7/Tatum-T Second Cover, 1  Flagyl 41, 42, Third Cover
Johns Hopkins University School of Medicine, The  Course 41	Syntex Norinyl 1+50 27, 28
Kaiser/Prudential Health Plan Opportunity Available 41	University Associates for International Health Incorporated Opportunity Available 20
Louisiana State University Medical Center Opportunity Available 10	University of Florida College of Medicine, The Opportunity Available 26
Mead Johnson Pharmaceutical Division Peri-Colace Fourth Cover	University of North Carolina at Chapel Hill, The Opportunity Available 20
Merck, Sharp & Dohme  Mefoxin 2, 3, 4  Urecholine 37, 38	Whitehall Laboratories  Preparation H 29

# available for the first time

The ten-year cumulative author and subject index to volumes 100-129 (1968-1977) of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY is now available for your journal collection. It is a complete and comprehensive reference guide to over 28,000 pages of authoritative articles published in the Journal during the past ten years.

The world-renowned "Gray Journal" is the oldest specialty journal devoted to obstetrics and gynecology.

Now these influential papers, appearing between 1968-1977, have been cross-referenced to include over 23,100 subject entries. Each entry lists the complete article title, author(s), volume, page, and year of publication.



The author index lists more than 13,850 contributors from this period, along with respective article title, author-to-author referral, volume, page, and publication date.

The 479-page index is handsomely presented in a rust and gold cloth-cover volume. It is a must for every library concerned with obstetrics and gynecology. Send for your copy of this valuable reference today!

479 pages, 81/4" × 11", Price: \$31.75 U.S.A.; \$40.25 Canada; \$33.50 all other countries.

# YES!

Send me \_\_\_\_ copies of the Ten-year Cumulative Index (1968-1977) to the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY (0126-6). Price: \$31.75 U.S.A.; \$40.25 Canada; \$33.50 all other countries.

Name \_\_\_\_\_ Bill me later. (I understand a shipping and handling charge will be added.)

City \_\_\_\_ State \_\_\_\_ Zip \_\_\_

Complete and mail today to The C. V. Mosby Company, Attn: Order Processing Dept., 11830 Westline Industrial Drive, St. Louis, Mo. 63141

# COMMUNICATIONS IN BRIEF

This section is suitable for reporting results of therapeutic trials, descriptions of new procedures or instruments, and case reports which illustrate a principle. Reports should be limited to seven hundred words and two references. Use of an illustration or table requires a proportionate reduction in total words.

Effect of in utero intravenous administration of thyroxine and other hormones on the lung fluid lecithin/sphingomyelin ratio in the fetal lamb

UCHENNA C. NWOSU, M.D.
ENDLA K. ANDAY, M.D.
RONALD J. BOLOGNESE, M.D.
ALFRED M. BONGIOVANNI, M.D.
MARIA DELIVORIA-PAPADOPOULOS, M.D.

Department of Obstetrics and Gynecology, Pennsylvania Hospital, the Departments of Medicine, Physiology, and Pediatrics, University of Pennsylvania School of Medicine, and the Endocrine Division, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

ALTHOUGH ANIMAL STUDIES have shown that glucocorticoids or thyroxine in pharmacologic doses can accelerate the appearance of pulmonary osmiophilic granules in the fetus, little is known of the effects of these hormones on the lecithin/sphingomyelin (L/S) ratio in the lung fluid or amniotic fluid.

To study the effect of certain glucocorticoids and iodothyronines on the lung fluid L/S ratio when directly administered to the fetus, nine lambs, at 113 to 124 days' gestation, were chronically catheterized in utero. A Foley catheter was anchored in the fetal trachea via a tracheotomy. After 3 to 12 days of postoperative

Supported by Pennsylvania Hospital General Research Grant No. RR 05590 and United States Public Health Service 5 22115-214.

Reprint requests: Dr. Uchenna Nwosu, Department of Obstetrics and Gynecology Faculty of Health Sciences, University of Ile-Ife, Nigeria. stabilization, they were divided into groups (Table I). The daily L/S profile for each fetal lamb was compared to mean daily values derived from seven control animals given pulses of physiologic saline at comparable periods of gestation.

The fetal blood pH remained within the normal physiologic range throughout the study period. Results were as follows.

No significant change in the lung L/S ratio was observed either during or after cortisol injections. In one case, no phospholipids were detectable at the times of cortisol administration (Ewe No. 145). The two fetuses were delivered on day 139 and day 143, respectively, with the normal duration of gestation being 145 days.

No change in the L/S ratio was apparent in one fetus during or after initial dexamethasone treatment and following repreated treatment 10 days later. Premature delivery occurred on day 134.

A significant rise in the L/S ratio occurred during the second course of thyroxine injection in two fetuses; peaks of 7:1 and 5:1, respectively, were reached on day 131. No phospholipids were detectable after day 135 in one of these animals (Ewe No. 400). The fetuses were delivered at term. Administration of thyroxine during the second period alone in another animal caused no change in the L/S ratio and delivery occurred at term.

Administration of triiodothyronine intravenously to one fetus (Ewe No. 360) resulted in immediate fetal death, probably due to triiodothyronine-induced fibrillation and cardiac arrest. No change in the L/S pattern occurred following treatment with smaller doses of triiodothyronine during the second period alone. Delivery of the fetal lambs occurred on days 145 and 139, respectively.

The mean fetal serum cortisol concentration a half hour after the administration of 2.5 mg of cortisol was 7.8  $\mu$ g/dl, decreasing to 0.6  $\mu$ g/dl in 24 hours. During

Table I. Hormone administration schedule

Gestational		First period		Second period		
Ewe No.	age at operation (days)	Hormone administered	Dose given	Gestational age (days)	Dose given	Gestational age (days)
145	113	Cortisol	2.5 mg	120, 121, 122	5.0 mg	130, 131, 132
379	119	Cortisol	_ 0	_	5.0 mg	130, 131, 132
185	116	Dexamethasone	200 μg	120, 121, 122	200 μg	130, 131, 132
300	113	Thyroxine	500 μg	119, 120, 121	500 μg	129, 130, 131
302	113	Thyroxine	500 μg	119, 120, 121	500 μg	129, 130, 131
381	119	Thyroxine		119, 120, 121	500 μg	129, 130, 131
360	114	Triiodothyronine	150 μg	119, —		_
323	124	Triiodothyronine		The same	1 μg	129, 130, 131
306	120	Triiodothyronine	- 51	·	10 μg	129, 130, 131

the second period, administration of 5 mg cortisol resulted in levels of 21 and 9  $\mu$ g/dl at one half hour and 24 hours, respectively. The normal mean fetal serum cortisol level prior to the cortisol surge is 1  $\mu$ g/dl, rising to 8  $\mu$ g/dl at the peak of the natal surge. The mean level over the entire second pulse period of 72 hours exceeded the maximum cortisol concentration of the physiologic surge of this hormone.

The mean level of triiodothyronine after administration of 1  $\mu$ g of triiodothyronine was less than 30  $\mu$ g/dl, similar to the normal level at this length of gestation. However, the mean 30-minute level of triiodothyronine after a 10  $\mu$ g dose exceeded 500  $\mu$ g/dl and decreased to 90  $\mu$ g/dl in 24 hours. Following the administration of 150  $\mu$ g of triiodothyronine, the serum level exceeded 1,000  $\mu$ g/dl.

Rapid surfactant production in the ovine fetal lung is known to occur between 120 and 126 days of gestation. Therefore, the time of hormone administration to the fetus was selected to correspond to this critical period. The failure of cortisol or dexamethosone to enhance the lung fluid L/S ratio, even when given in sufficient doses to cause premature delivery, was unexpected. We cannot explain the disappearance of detectable levels of phospholipids during cortisol treatment in view of the previously observed increase of osmiophilic granules in the fetal lung following glucocorticoid administration.

In contrast to glucocorticoids, the present data suggest that pharmacologic doses of thyroxine can alter the lung fluid L/S ratio provided the fetus has been previously primed. A priming dose may be required to induce thyroxine receptors. This finding is consistent with the observation of Wu and colleagues² that the in utero intramuscular administration of thyroxine to the fetal rabbit in late pregnancy resulted in increased surface activity of alveolar washings. Further study regarding the pharmacologic use of thyroxine for acceleration of fetal lung maturation appears to be justified.

# REFERENCES

 Platzker, A. C. G., Kitterman, J. A., Tooley, W. H., Mescher, J. E., and Clements, J. A.: Surfactant in the lung and tracheal fluid of the fetal lamb and acceleration of its appearance by dexamethasone, Pediatrics **56**:554, 1975.

 Wu, B., Kikkawa, Y., Orzalesi, M. M., Motoyama, I. E., Kaibara, M., Zigas, C. J., and Cook, C. D.: Accelerated maturation of fetal rabbit lungs by thyroxine, Physiologist 14:253, 1971.

# L-5 Radiculopathy secondary to a uterine leiomyoma in a primigravid patient

L. P. M. HEFFERNAN, M.D., F.R.C.P.(C.)

R. C. FRASER, M.D., F.R.C.S.(C.)

R. A. PURDY, M.D., F.R.C.P.(C.)

Departments of Medicine and Obstetrics and Gynecology, Dalhousie University, Halifax, Nova Scotia, Canada

A CASE REPORT of a primigravid patient with L-5 radiculopathy is presented.

A 28-year-old primigravid patient presented at 22 weeks' gestation with the recent onset of painless swelling of the entire left leg, weakness of left ankle dorsiflexion, eversion, inversion, toe dorsiflexion, and impaired pinprick sensation in the web space between the great and second toes. Abdominal assessment revealed the uterus to be markedly irregular because of fundal masses. Pelvic examination demonstrated the cervix and uterus to be pushed up and forward by a large soft tender mass filling the pouch of Douglas.

Motor and sensory conduction study of the left peroneal and sural nerves demonstrated only a reduction in the evoked motor potential amplitude, indicating a fallout of the motor unit population, with the surviving units conducting normally. Monopolar needle electrode assessment demonstrated, in the pattern outlined (Table I), evidence of abnormal spontaneous activity indicative of denervation and neurogenic motor unit alterations. Such changes indicated the presence of partial axonal degeneration.

Ultrasonography demonstrated a large mass (8 by 10 cm) in the region of the posterior uterine wall abutting against the

Reprint requests: Dr. L. P. M. Heffernan, Room 210 Pavilion, Victoria General Hospital, Halifax, Nova Scotia, Canada B3H 2Y9.

sacrum, felt to represent either a subserosal leiomyoma or possibly a retrouterine malignancy. As malignant neoplasia could not be excluded, a laparotomy was deemed necessary. The gravid uterus was found to be markedly irregular and distorted due to the presence of multiple leiomyomas of varying sizes, including the huge growth which was indeed located on the posterior wall. The following day premature labor ensued. Vaginal delivery was performed, but the fetus did not survive. Venography was subsequently performed and demonstrated evidence of marked obstruction in the pelvis and the deep veins of the left lower extremity. Shortly thereafter the leg swelling began to abate and no progression of the neurological deficit ensued.

The detection at clinical examination of weakness of inversion placed the site of dysfunction outside the territory of the peripheral peroneal nerve, peroneal palsy being the usual cause of weakness solely of dorsiflexion and eversion. Weakness of all three movements suggested impairment of a shared innervation which must be proximal, i.e., radicular, and not distal in view of the sparing of the plantar flexor movement. The pattern of clinical weakness was indicative of L-5 dysfunction. Denervation (abnormal spontaneous activity manifested by positive waves and fibrillation potentials) and neurogenic alterations of the motor units result from a loss of axonal continuity. The presence of such changes in certain muscles outside of the territory of a single peripheral nerve most often indicates dysfunction of a shared proximal radicular innervation. The changes detected in this patient, on the basis of previous work from this laboratory,1 indicated L-5 to be the damaged radicle, confirming the clinical impression. The absence of denervation in the appropriate paraspinal musculature indicated that the problem must be located distal to the takeoff of the posterior primary rami, i.e., at an extraspinal site. This, combined with involvement of a proximal muscle, i.e., tensor fasciae latae, strongly indicated that the dysfunction was located at a retroperitoneal site.

The fibers of L-5, in order to reach the sacral plexus (which lies in the true pelvis), must cross over the sacral ala at the level of the pelvic inlet. The L-5 root at this point has emerged from beneath the protecting covering of the overlying psoas muscle and thus lies completely exposed. The gravid uterus plus a huge posterior leiomyoma was sufficient in concert to bring compromising pressure to bear on the exposed L-5 root at this level, which resulted in the clinical and electrical dysfunction. The subsequent spontaneous labor and uterine involution obviously provided sufficient decompression, which correlated with resolution of the leg swelling and lack of clinical progression of the neurological dysfunction. The patient underwent an abdominal hysterectomy 3 months after delivery and pathologic verification of the leiomyomatous nature of the mass was provided.

That this is indeed a rare and an unusual neurological complication of such a common benign uterine

Table I. Needle electrode assessment

Muscle	Abnormal spontaneous activity*	Motor unit potentials
Left tibialis anterior	+++	Neurogenic
Left tibialis posterior	+++	Neurogenic
Left peroneal group	+++	Neurogenic
Left tensor fasciae latae	+	Neurogenic
Left lateral gastrocnemius	±	Normal
Left medial gastrocnemius	0	Normal
Left vastus lateralis	0	Normal
Left gluteus medius	0	Normal
Left paraspinals L-3 to S-1	0	

 $<sup>0 =</sup> Normal. \pm Through +++ = minimal to excessive ac-$ 

neoplasm is attested to by the fact that a detailed literature review of the complications of fibroids, including those of massive proportions, although often stressing the occurrence of back and leg pain, made no mention of definite radicular dysfunction productive of sensory loss and weakness. A recent monograph<sup>2</sup> on the neurological complications of pregnancy also made no mention of this possibility.

# REFERENCES

- 1. Heffernan, L. P.: Electromyographic value of the tibialis posterior muscle, Arch. Phys. Med. Rehabil. 60:170, 1979.
- Donaldson, J. O.: Neurology of Pregnancy: Major Problems in Neurology Series, Philadelphia, 1978, vol. 7, W. B. Saunders Company, p. 43.

# Fluorescein angiography in hypertensive pregnancies

- B. DONKERS
- D. JANSONIUS

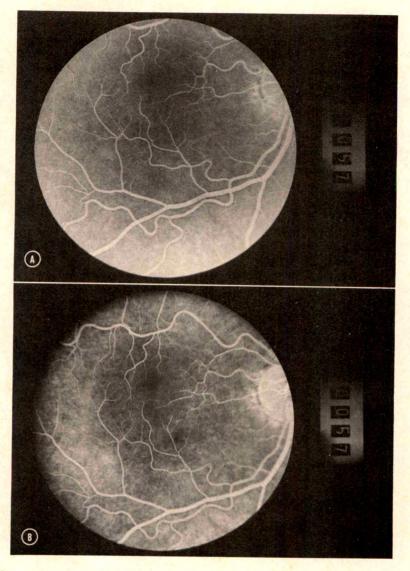
Department of Obstetrics and Gynecology and Department of Ophthalmology, St. Geertruiden Gashuis of Ziekenhuis, Deventer, The Netherlands

VASCULAR CHANGES seen in the retina are presumed to reflect systemic vascular changes. Examination of the vascular patterns of the eye grounds is very useful in management of toxic gravid patients. However, these vascular changes have been difficult to understand.1

Fluorescein angiography has added a new dimension to clinical examination of the ocular fundus.2 Advantages of this method are: (1) an increased ability to

Reprint requests: Dr. B. Donkers, vrouwenarts, Afdeling Obstetrie en Gynaecologie, St Geertruiden Gasthuis of Ziekenhuis, Fesevurstraat 7, 7415 CM Deventer, The Netherlands.

<sup>\*</sup>Positive waves and/or fibrillation potentials.



**Fig. 1.** Fluorescein angiography of the ocular fundus in Patient B. A: Nineteenth week of pregnancy; B: thirty-ninth week of pregnancy. Note increased areas with vascular leakage.

detect abnormalities, even in the small capillaries, and (2) the capability to perform flow pattern studies with the use of serial photography at a fixed frequency. As disadvantages, some patient discomfort (nausea, vomiting), expense of the apparatus, and the length of the procedures are to be mentioned.

The purpose of this brief paper is to report preliminary results with this method of examination in the investigation of changes in the vascular tree during pregnancies complicated by hypertensive disorders.

To investigate the usefulness of the method, first a group of seven patients was examined during clinical observation (one examination per patient). Examination was done in three patients in the first half of pregnancy, in three patients in the second half of pregnancy, and in one patient in the postpartum period. Patients were selected because of their previous history

(hypertensive disorders in pregnancy, eclampsia, or abruptio placentae). In the current pregnancy the patients had blood pressures of RR 140/90 mm Hg or more, with or without proteinuria and/or edema.

Ophthalmoscopic examination with the pupils dilated was performed. After an intravenous injection of 5 ml of 15% sodium fluorescein, funduscopy was done with a special camera (Topcon TRC/F); serial photography, at a fixed frequency of two per second, was started immediately after the injection and ended after the retinal veins became uniformly fluorescent.

Fluorescein angiography of the ocular fundus enabled follow-up studies of changes in peripheral vascular patterns to be much better than with normal ophthalmoscopy.

The fluorograms of patients with persistent hypertension post partum showed hypertensive disor-

Table I. Fluorescein angiography in hypertensive pregnancies ("toxemia")

Pa- tient	History	Blood pressure	Protein excretion (mg/24 hr)	Edema	Fluorescence angiography		
					A	В	Conclusion
A B	Hypertension, gravida 1, child normal Gravida 3.	180/120	740	±	Six months before pregnancy	37 weeks	Increased hyper- tensive disorders
С	First pregnancy—abortion Second pregnancy—toxemia and hypertension post partum Third pregnancy—twins Children normal Gravida 2.	140/90	200	+ to ++	19 weeks	39 weeks	Increased hyper- tensive disorders
	First pregnancy—intrauterine death, abruptio placentae Second pregnancy—child normal	140/90	<150	-	10 weeks	35 weeks	Normal, no changes
D E	Gravida 2. First pregnancy—toxemia Second pregnancy—child normal Gravida 2.	170/90	350	±	21 weeks	30 weeks	Moderate hyper- tensive disorders, no changes
~	First pregnancy—toxemia and eclampsia imminens Second pregnancy—child small for date	140/90	<150	±	16 weeks	35 weeks	Moderate hyper- tensive disorders, no changes

ders, whereas in patients with normal blood pressures after delivery ("transient" hypertension) there were no abnormalities. Patient discomfort was acceptable; one examination had to be stopped because of nausea and vomiting of the patient after the intravenous injection of fluorescein. Other disturbances in maternal or fetal function (liver function, kidney function, hematologic systems, maternal plasma estriol level and estriol excretion, antepartum cardiotocography) were not seen. After birth examination of the children showed no congenital malformations.

To prove that application of fluorescein angiography was superior in the differential diagnosis of hypertension in pregnancy, a group of five patients was examined twice (Table I). The number of patients is too small to make any conclusions; however, observations point to the possibility that vascular abnormalities increase during pregnancy in patients with so called superimposed hypertension (Fig. 1), whereas they do not in patients with so-called transient hypertension.

Fluorescein angiography of the ocular fundus appeared to be very useful in follow-up studies concerning the behavior of peripheral capillaries in patients with hypertensive disorders in pregnancy. Further investigation is to be done on different changes developing during pregnancy.

#### REFERENCES

1. Finnerty, F. A., Jr.: Does vascular damage follow toxemia of pregnancy? JAMA 154:1075, 1954.

Novotny, H. R., and Alvis, D. L.: Method of photographing fluorescence in circulating blood in the human retina, Circulation 24:82, 1961.

### The "female echo": Prenatal determination of the female fetus by ultrasound

ANNEMARIE SCHOTTEN CHRISTA GIESE

Department of Obstetrics and Gynecology, Marienhospital Aachen, Aachen, West Germany

UNTIL NOW the only possibility of prenatal determination of fetal sex by ultrasound was the demonstration of the fetal perineal area with or without the scrotal image. Female genitalia could be distinguished by ultrasound only in cases of enlargement of these organs, e.g., enlargement of the uterus1 and the presence of ovarian cysts2.

Female external genitalia can be demonstrated as follows: On a transverse scan of the fetal perineal area, the "female echo" can be seen between the thighs in the level of the bladder (Figs. 1 and 2). There are three or four parallel lines vertical to the longitudinal axis of the fetus. The exterior lines show the labia majora; the inner one or two lines, the labia minora. If these are not too close together, two separate echos can be distinguished.

In growth-retarded female fetuses, the labia majora are often rather prominent. In these cases it may be difficult to distinguish them from small testes. We demonstrated this characteristic echo pattern from the

Reprint requests: Dr. Christa Giese, Department of Obstetrics and Gynecology, Marienhospital Aachen, Zeise 4, D-5100 Aachen, West Germany.

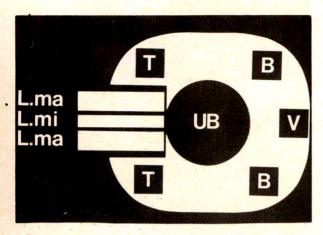


Fig. 1. "Female echo." Drawing of a transverse scan at the level of the bladder. T: Proximal thigh. B: Buttocks. UB: Urinary bladder. V: Spine (sacral region). L.ma: Labia majora. L.mi: Labia minora.



Fig. 2. Transverse scan showing the "female echo." The fetus is in the first cephalic position.

twenty-third week of gestation onward. Thus, demonstration of the female external genitalia by ultrasound is a direct method of female sex determination.

#### REFERENCES

- 1. Schotten, A.: In Kratochvil, A., editor: Ultraschalldiagnostik, Stuttgart, 1978, E. Reinold Thieme, p. 93.
- 2. Leh, T. G., and Blake, S.: Prenatal fetal abdominal ultra-. sonography and diagnosis, Radiology 124:475, 1977.

## Ultrasonographic diagnosis of fetal cystic hygroma

WILLIAM F. O'BRIEN, LIEUTENANT COMMANDER, MC, USNR ROBERT C. CEFALO, M.D., Ph.D. DONALD G. BAIR, LIEUTENANT, MC, USNR

Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, National Naval Medical Center, Bethesda, Maryland

ALTHOUGH INTRAUTERINE nuchal cystic hygroma (lymphangioma) has been noted sonographically in the past, the correct diagnosis was ascertained only in retrospect. The sonographic and roentgenologic characteristics of the lesion were not sufficiently well recognized at the time of examination to assure diagnosis. Recently, an intrauterine cystic area was noted in two patients in whom ultrasonography was performed for obstetric dating. In the first case the diagnosis was not suspected and the patient was unprepared for the outcome. In the second patient, through the combined use of standard gray-scale ultrasonography, real-time ultrasonography, and roentgenography a diagnosis of cystic hygroma was made with high probability. The patient was informed of the diagnosis and the expected poor outcome of the pregnancy. She was able to be spared invasive procedures and the mental suffering of uncertainty.

In Case 1, a 32-year-old white woman, gravida 4, para 1, abortions 2, had an ultrasonographic examination at 24 weeks' gestation for dating (size larger than expected). A large cystic mass was noted in the posterior nuchal region with septa noted within the cyst (Figs. 1 and 2). The cranial vault appeared intact. This area was diagnosed as a blighted twin with residual amniotic cavity. Fetal biparietal diameter was consistant with a 21.5 weeks' gestation and fetal heart motion was present. Ten days following examination the patient entered another hospital because of premature labor. Fetal heart tones were not audible on admission and the patient was delivered of a 1,340 gm stillborn edematous female infant. A large cystic area was noted in the nuchal region and Turner's syndrome was suspected by a consulting geneticist.

In Case 2, a 22-year-old white woman, gravida 2, para 1-0-0-1, had an ultrasonographic examination at 23 weeks' gestation for obstetric dating (size greater than expected). Standard gray-scale examination revealed a large cystic area with septation in the posterior nuchal region (Fig. 3). Realtime ultrasonography revealed heart motion and a constant

The opinions expressed herein are solely those of the authors and are not to be construed as reflecting the opinions of the Department of Defense or the Navy Department.

Reprint requests: William F. O'Brien, Lieutenant Commander, MC, USN, Department of Obstetrics and Gynecology, National Naval Medical Center, Bethesda, Maryland 20014.

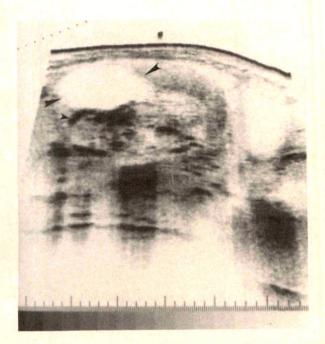


Fig. 1. Large cystic mass in the posterior nuchal region with septa within cyst.

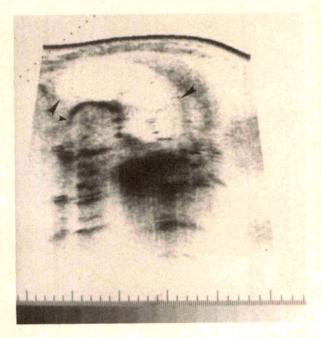


Fig. 2. Large cystic mass in the posterior nuchal region with septa within cyst.

location of the cystic area with regard to the fetus. Roentgenography failed to demonstrate a defect in the cranium.

The patient was advised of the high probability of cystic hygroma and the possibility of second-trimester fetal death. On examination 1 week later no fetal heart motion was noted. Three weeks following documentation of intrauterine fetal death the patient underwent induction of labor with prostaglandin E vaginal suppositories and was delivered of a 560 gm

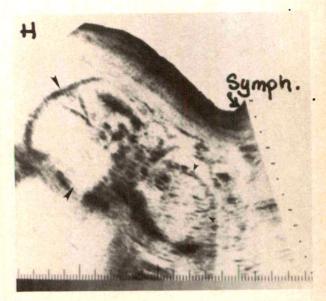


Fig. 3. Large cystic area with septa in posterior nuchal region.



Fig. 4. Fetus following intrauterine death, weighing 560 gm, with cystic hygroma.

stillborn female infant. Diagnosis of cystic hygroma was confirmed at autopsy (Fig. 4).

In 1966, Singh and Carr¹ noted a characteristic combination of defects in abortuses with XO genotypes. These abortuses were phenotypically female and exhibited generalized edema and large cystic hygromas in the posterior nuchal region. Characteristically abortion had occurred between 123 and 159 days' gestational age (19.5 and 24.7 weeks' menstrual age). Since this original report a number of series have substantiated the pattern of cystic hygroma, generalized edema, failure of ovarian follicular development, and spontaneous abortion of a macerated fetus during the second trimester of pregnancy. When karyotypic analyses have been possible in these fetuses XO monosomy is found.

The ultrasonographic characteristics leading to the correct intrauterine diagnosis of this entity should include the following: at least two bilaterally symmetrical echo-free areas in the posterior nuchal region, usually divided by septa; a completely formed cranial vault; and constant location of the masses with respect to the occiput despite fetal motion. The position and presence of septa should weigh against alternative possible diagnoses such as meningomyelocele and benign cystic teratoma. An intact cranial vault excludes encephalocele. The constant position of the structures with regard to the occiput excludes the possibility of subchorionic placental cyst.

Amniotic fluid alpha fetoprotein has been noted to be elevated in association with cystic hygroma. The mechanism of this association is unknown at present and it has been postulated that the elevation is due to the enlarged surface area or the increased interstitial fluid pressure felt to be present in these fetuses. The rather striking size of the cystic area noted at sonography suggests an additional possibility. Unless the borders of the echo-free areas are noted and the anomaly suspected, the sac may be felt to be a pocket of amniotic fluid and aspirated or punctured. Direct cyst puncture after abortion yielded alpha-fetoprotein levels similar to the high levels found in fetal serum.<sup>2</sup>

High prenatal suspicion of this diagnosis may also facilitate postnatal diagnosis as samples for karyotype analysis from multiple sources of the fetus and the placenta can be utilized. Although second-trimester fetal death occurred in both cases reported, it is possible that similar findings may be present in gestations which result in viable infants with Turner's syndrome.

#### REFERENCES

- Singh, R. P., and Carr, D. H.: The anatomy and histology of XO human embryos and fetuses, Anat. Rec. 155:369, 1966.
- Pawlowitzki, I. H., and Wormann, B.: Elevated amniotic alpha fetoprotein in a fetus with Turner's syndrome due to puncture of a cystic hygroma, Am. J. Obstet. Gynecol. 133:584, 1979.

# The effect of maternal dietary fat on fetal pulmonary maturation in rats

GEORGE H. NELSON, M.D., PH.D.
JAMES McPHERSON, JR., M.D.
LANCE PERLING, B.S.
RICK CIECHAN, B.S.

Departments of Obstetrics and Gynecology and Surgery, Medical College of Georgia, Augusta, Georgia

WE HAVE PREVIOUSLY shown<sup>1</sup> that the measurement of acetone-precipitable lecithin (APL) concentration in fetal lung tissue is an excellent model for evaluation of fetal pulmonary maturation. Gestational age, dexamethasone, and Metopirone<sup>1</sup> have been shown to influence lung maturation, whereas hypoxia<sup>2</sup> has no effect.

It is well established that the main component of pulmonary surfactant (likewise APL) is dipalmitoyl lecithin. We hypothesized that the maternal dietary intake of palmitic acid may affect fetal lung maturation by restricting or not restricting the fetal supply for synthesis of surfactant. These experiments were designed to test this hypothesis.

The methodology used for dating the pregnancies and for APL analysis has been previously reported.1 Adult female rats were randomly assigned to one of three diets: fat-free (FF), 10% corn oil (CO), or 10% palm oil (PO). A basic diet was prepared with 21.0% casein, 16.5% alphacel, 58.5% sucrose, and 4.0% salt mixture. An adequate supply of all vitamins was thoroughly mixed into the basic diet. The experimental diets were made up as follows: FF, 900 gm basic diet plus 225 gm of sucrose; CO, 900 gm basic diet plus 100 gm of corn oil; PO, 900 gm basic diet plus 100 gm of palm oil. The corn oil was purchased locally and contains approximately 10% palmitic acid and 48% linoleic acid. The palm oil was obtained from PVO International, Inc., St. Louis, Missouri, and contains approximately 46% palmitic acid and 9% linoleic acid. The diets contained the same quantity of protein per caloric equivalent. The rats were fed ad libitum for at least 3 weeks prior to conception and throughout gestation.

Accurate measurements of daily food intake were not made; however, there was no indication from refilling the food cups that the rats on the different diets consumed a grossly different amount of food. Previous work by Adolph<sup>3</sup> also has shown that rats tend to consume the same number of daily calories when the caloric content of the diet is varied.

The rats were killed on gestational days 18, 20, and 21, and the body weights in grams (maternal weight

Reprint requests: Dr. George H. Nelson, Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta, Georgia 30912.

**Table I.** Concentration of acetone-precipitable lecithin in fetal lung tissue from rats on FF, CO, or PO

Gestational Day	Diet	Mean ± SD of 6-9 analyses (pooled samples)	Significance*
18	FF	$11.9 \pm 3.0$	
	CO	$13.3 \pm 1.2$	CO vs. FF, NS
	PO	$13.6 \pm 1.7$	PO vs. FF, NS;
			PO vs. CO, NS
20	FF	$14.8 \pm 1.6$	
	CO	$17.1 \pm 3.4$	CO vs. FF, NS
	PO	$21.0 \pm 1.8$	PO vs. FF, $p < 0.05$ ;
			PO vs. CO, $p < 0.05$
21	FF	$14.9 \pm 2.2$	
	CO	$19.3 \pm 1.3$	CO vs. FF, $p < 0.05$
	PO	$25.0 \pm 3.3$	PO vs. FF, $p < 0.05$ ;
			PO vs. CO, p < $0.05$

<sup>\*</sup>NS: Not significant.

prior to cesarean section minus litter weight, mean  $\pm$  SD) of the dams were as follows: gestational day 18, FF 293  $\pm$  8, CO 281  $\pm$  39, PO 321  $\pm$  31; gestational day 20, FF 302  $\pm$  19, CO 275  $\pm$  26, PO 334  $\pm$  35; gestational day 21, FF 276  $\pm$  73, CO 300  $\pm$  34, PO 284  $\pm$  29. While these animals were not weighed prior to their respective diets, the above data do not suggest in any way that the dams refused any of the diets.

The numbers of dams and pups in each group were: gestational day 18, FF 8 and 74, CO 6 and 72, PO 6 and 81; gestational day 20, FF 3 and 36, CO 5 and 51, PO 5 and 49; gestational day 21, FF 5 and 30, CO 3 and 37, PO 4 and 33.

The pup weights in grams (mean  $\pm$  SD) at delivery were: gestational day 18, FF 1.20  $\pm$  0.11, CO 1.17  $\pm$  0.12, PO 1.15  $\pm$  0.11; gestational day 20, FF 2.95  $\pm$  0.29, CO 3.13  $\pm$  0.27, PO 2.88  $\pm$  0.31; gestational day 21, FF 4.48  $\pm$  0.48, CO 4.46  $\pm$  0.33, PO 4.87  $\pm$  0.68. As can be seen, at the three gestational days a different diet for each day was associated with the largest mean pup weight. Therefore, no diet regimen was consistently associated with smaller pup weights, again suggesting that the quantity of food consumed by the dams was not a significant variable in these experiments.

Pooled samples (0.3 to 0.6 gm) of fetal lung tissue were analyzed for APL and the results are shown in Table I as milligrams of APL phosphorus per 100 gm of tissue. Statistical differences were determined by means of Student's t test.

As can be seen, the increase in APL concentration is less during the last 3 days of gestation in the absence of maternal dietary fat than with the fat-containing diets. In addition, rats had significantly increased APL on gestational days 20 and 21 on the PO diet when compared to the CO diet. One can only surmise that this latter difference is due to the palmitic acid content.

These data provide interesting speculation regarding human pregnancy. One might logically wonder

whether newborn infants of mothers who are on a low palmitic acid diet might be more susceptible to the development of respiratory distress syndrome than newborn infants of mothers who are not on such a diet. One might also speculate on the feasibility of using a palmitic acid—rich dietary supplement in pregnant women prior to elective induction of labor or cesarean section in order to ensure adequate substrate for surfactant synthesis. Further study along these lines would appear to be definitely indicated.

While dietary saturated fat has for many years been in ill repute in the medical and nutritional literature, this may be one instance in which it may be superior to its unsaturated counterpart. Only time will provide the answer.

#### REFERENCES

- Nelson, G. H., Eguchi, K., and McPherson, J. C.: Effects of gestational age, dexamethasone, and Metopirone on lecithin concentration in fetal lung tissue and amniotic fluid in rats and guinea pigs, Gynecol. Invest. 7:337, 1976.
- Nelson, G. H., McPherson, J. C., and Eguchi, K.: Effect of hypoxia on lecithin concentration in fetal lung tissue and amniotic fluid in rats, Am. J. Obstet. Gynecol. 132:226, 1978.
- Adolph, E. F.: Urges to eat and drink in rats, Am. J. Physiol. 151:110, 1947.

# Serial ultrasonographic biparietal diameters for prediction of estimated date of confinement

WILLIAM F. O'BRIEN, LIEUTENANT
COMMANDER, MC, USNR
CHARLES C. CODDINGTON, LIEUTENANT,
MC, USN
ROBERT C. CEFALO, M.D., Ph.D., F.A.C.O.G.

Departments of Obstetrics and Gynecology, National Naval Medical Center, Bethesda, Maryland, and the University of North Carolina, Chapel Hill, North Carolina

CURRENT RECOMMENDATIONS for the management of high-risk pregnancies often include the use of serial sonographic determination of the fetal biparietal diameter (BPD). In addition to information obtained on the rate of fetal growth, serial examinations are felt to provide a check on the accuracy of a single reading.<sup>1</sup>

The opinions and assertions contained herein are those of the authors and are not to be construed as official or as representing those of the Bureau of Medicine and Surgery of the Department of the Navy or of the Naval Service at large.

Reprint requests: William F. O'Brien, Lieutenant Commander, MC, USNR, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, National Naval Medical Center, Bethesda, Maryland 20014.

Table I. Accuracy of prediction: First and second examinations and arithmetic mean (days)

	First	Second	Mean	Probability
Gestational age (mean ± SD) Actual error (mean ± SD) Absolute error (mean ± SD)	$21.7 \pm 2.9$ $-2.1 \pm 10.8$ $8.3 \pm 7.1$	$26.7 \pm 2.6$ $-0.94 \pm 10.9$ $8.4 \pm 6.9$	$-1.6 \pm 9.8$ $-1.2 \pm 6.7$	p < 0.01 p > 0.05 p > 0.05

<sup>\*</sup>Unpaired Student's t test

The present study was designed to evaluate the efficacy of a second BPD between 18 and 30 weeks' gestation in the prediction of onset of labor.

The study group consisted of 50 consecutive patients who had at least two BPD determinations between 18 and 30 weeks' estimated gestational age (as determined by measurement of BPD). All studies were conducted during 1978 at the National Naval Medical Center and only patients who subsequently entered spontaneous labor were included. Dubowitz scores on all infants were consistent with term pregnancy (>38 weeks' gestational age). Ultrasonographic examinations were performed by trained technicians under the guidance of staff radiologists. All scans were performed with the Picker System 80L-D1 system.\* Determinations of BPD were made with B-mode ultrasonography from leading edge to leading edge and measured with electronic calipers. Estimations of gestational age were made from a table of composite means of previous reports.<sup>2</sup>

Accuracy of prediction was determined by analysis of the difference between the sonographically predicted estimated date of confinement (EDC) and the date of onset of spontaneous labor. Actual error (prediction earlier than labor expressed as a negative error and one later than labor expressed as a positive error) and absolute error (discrepancy in either direction) were calculated for the first and second scans, and the arithmetic mean of two values was determined. All errors were expressed in days (Table I). Comparisons were made by means of the unpaired t test with significance accepted as p < 0.05.

Results indicate that the combined result of both examinations did not add to the accuracy of EDC prediction. Although the absolute error was reduced by a mean of 1.2 days when results were combined, a study population of over 300 patients would be required to establish this difference as statistically significant.

The use of sonographic determinations of BPD has become an integral part of current obstetric practice. Most authors have recommended that for optimal value these assessments must be begun prior to the thirtieth week of pregnancy. Multiple determinations of the fetal BPD have been recommended in a number of clinical situations in which accurate prediction of fetal age is important. Although the use of serial

\*Picker Corporation, 12 Clintonville Road, Northford, Connecticut.

sonography may aid the clinician in the evaluation of the fetus at risk for intrauterine growth retardation (IUGR), the present study fails to demonstrate that a second BPD determination prior to 30 weeks' gestation significantly improved the prediction of the EDC.

It is concluded, therefore, that unless a more complex system such as the GASA method as described by Sabbagha and associates,<sup>2</sup> is utilized or IUGR is suspected, a single BPD determination between 18 and 30 weeks' gestational age is sufficient for predicting the estimated date of confinement. This will spare the patient the expense and inconvenience of a second examination.

#### REFERENCES

- 1. Hobbins, J. C., and Winsberg, F.: Ultrasonography in Obstetrics and Gynecology, Baltimore, 1977, The Williams & Wilkins Co., p. 47.
- Sabbagha, R. E., and Hughey, M.: Standardization of sonar cephalometry and gestational age, Obstet. Gynecol. 52:402, 1978.

#### Multiple pulmonary fibroleiomyomas

LUKE G. TEDESCHI, M.D.

Department of Pathology, Framingham Union Hospital, Framingham, Massachusetts, and Boston University School of Medicine, Boston, Massachusetts

MULTIPLE pulmonary leiomyomas are an extremely rare entity, with 12 well-documented cases recorded in the world literature<sup>1</sup> and 21 accumulated in the Averill A. Liebow Pulmonary Collection.<sup>2</sup> Despite the infrequency of this entity, it should be considered in the differential diagnosis of asymptomatic middle-aged women in whom a routine chest x-ray film is compatible with metastatic neoplasia.

This communication describes such a case with a 7-year follow-up.

A 37-year-old woman was admitted originally to the Dental Service for removal of a maxillary cyst. A routine preoperative

Reprint requests: Luke G. Tedeschi, M.D., Department of Pathology, Framingham Union Hospital, Lincoln St., Framingham, Massachusetts 01701.

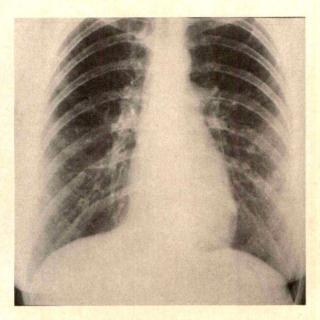


Fig. 1. Posteroanterior upright chest film showing multiple bilateral pulmonary nodules.



Fig. 2. Lung biopsy specimen revealing the presence of a well-demarcated nodule.

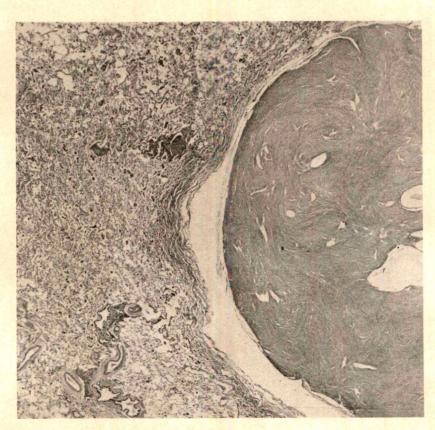


Fig. 3. Low-power view of lung with the circumscribed nodule composed of whorled and homogeneous small muscle cells. (Hematoxylin and eosin.  $\times 60$ .)

chest x-ray examination demonstrated bilateral multiple pulmonary nodules compatible with metastatic neoplasia (Fig. 1).

Her past medical history was noncontributory, with the exception of a hysterectomy 16 years previously for fibroids of the uterus. Unfortunately, the microscopic slides were not available for review nor were previous chest x-ray films obtainable.

The findings on physical examination were within normal limits, but because of the chest x-ray film, she underwent a battery of investigative studies, including mammography, gastrointestinal series, barium enema, intravenous pyelography, and a host of laboratory procedures as well as skin testing for bacteriologic and fungal organisms. Findings from all of the procedures were within normal limits.

Subsequently, a thoracotomy on the left side was performed which revealed the presence of multiple, small, firm pulmonary nodules that varied in size from 0.5 to 1.5 cm. in greatest diameter. One of the nodules was removed (Fig. 2) and examined histologically. It was composed of well-circumscribed smooth muscle cells (Fig. 3) arranged in fascicles of spindle-shaped cells with blunt, elongated nuclei and fibrillar eosinophilic cytoplasm within a well-vascularized stroma.

The patient's postoperative course was uneventful, and close follow-up has found that she is asymptomatic, with x-ray changes which suggest that the nodules are becoming smaller, most likely because of collagenization and scarring.

Review of the medical literature stresses two prevailing etiologies for this condition. The first is the designation of de novo multiple pulmonary hamartomas of the leiomyomatous type. A hamartoma is classically described as a tumor-like malformation that contains an abnormal mixture of tissue intrinsic to the site of origin. Ultrastructure examination has shown tubular

epithelial elements intermingled with the smooth muscle cell. Embryologically, this can be explained by the fact that the lung arises from entodermal buds branching into the primitive mesenchyme. Granted that most pulmonary hamartomas are single and of the chondromatous type, multicentricity and smooth muscle predominance are feasible.

The other theory shares with this case and all of the others in the literature several striking similarities which cannot be taken lightly. Mainly, all of the cases occurred in women, ages 31 to 63, who had undergone hysterectomy from 3 to 20 (mean, 10) years previously; and in 18 of 21 cases, benign leiomyomata were found in the hysterectomy specimens.<sup>2</sup> It is proposed that intravascular extension of cords and strands of benign myomatous tissue penetrates into the venous channels of the pelvis and subsequently spreads to the lungs. Similarly, the epithelium which had been described by ultrastructure most likely is entrapped respiratory epithelium.<sup>2</sup>

It must be emphasized, however, that meticulous microscopic examination of the uterine leiomyomas, as well as the pulmonary nodules, should be carried out so as to rule out metastatic low-grade leiomyosarcomas.

#### REFERENCES

- Nili, M., Vidne, B. A., Avidor, I., et al.: Multiple pulmonary hamartomas: A case report and review of the literature, Scand. J. Thorac. Cardiovasc. Surg. 13:157, 1979.
- Tench, W. D., Dail, D., Gmelich, J. T., et al.: Benign metastasizing leiomyomas: A review of 21 cases, Lab. Invest: 38:367, 1978. (Meeting Abstract.)

## CORRESPONDENCE

# Low-dose heparin in prevention of venous thromboembolism

To the Editors:

Low-dose heparin as a prophylactic method for prevention of venous thromboembolism has been acclaimed as a major advance in the prevention of this serious postoperative complication. Although early studies noted no significant bleeding sequelae of this "subclinical" dose of heparin, more recent articles have demonstrated that low-dose heparin may be associated with both laboratory and clinical coagulation defects. <sup>1-6</sup> Most recently, Chung and colleagues (Am. J. Obstet. Gynecol. 135:1025, 1979) reported no significant side effects of low-dose heparin. The article is worrisome, however, in that it is a small series (75 patients divided into three study groups) and it apparently disregards important information in previous articles on the subject.

Gurewich and colleagues<sup>4</sup> found that the partial thromboplastin time was prolonged greater than two times the control value in 15% and 10% of patients at 2 and 4 hours after 5,000 U of sodium heparin was injected subcutaneously. It is not surprising that Chung and associates did not find this since they checked the partial thromboplastin time at 24 and 72 hours postoperatively. The time relationship of heparin administration and the partial thromboplastin time were not noted in their article.

The time at which coagulation factors are evaluated also appears to be of importance in the evaluation of the incidence of thrombocytopenia induced by low-dose heparin. Galle and co-workers<sup>5</sup> and Hrushesky<sup>6</sup> reported four cases of profound thrombocytopenia attributed to low-dose heparin. The earliest recognized case occurred on the seventh day of heparin administration, while one was noted only after 22 days. Chung and associates did not find a significant change in platelet count but they only monitored their patients for 72 hours postoperatively.

Finally, with regard to clinically recognized bleeding complications, there have been many reports of excessive intraoperative and postoperative bleeding attributed to low-dose heparin. Most disturbing is the study of Pachter and Riles, in which there was a bleeding and wound complication rate of 27% in the heparin group compared to 1.4% in the control group. While Chung and associates noted that "there was no excessive clinical bleeding that could be attributed to hepa-

rin," they did not report what criteria confirmed this impression.

Low-dose heparin appears to offer significant benefits for thromboembolism prophylaxis in high-risk groups. The risk of hemorrhage with this therapy is important to all surgeons and especially the obstetrician and gynecologist who often cares for patients at low risk for thromboembolic complications. Whether the risk of hemorrhage outweighs the benefit of thromboembolism prophylaxis (or vice versa) needs to be established in large, well-designed studies. However, the article by Chung and associates contributed nothing to our understanding of the potential risks of coagulation defects caused by low-dose heparin. Further, it seems irresponsible to report that the use of 5,000 U of subcutaneous heparin every 12 hours has no significant risk of hemorrhagic complications based on the meager experience of 31 patients whose assessment of coagulation defects was improperly timed.

Daniel L. Clarke-Pearson, M.D.

Division of Gynecologic Oncology Department of Obstetrics and Gynecology Duke University Medical Center Durham, North Carolina 27710

#### REFERENCES

- Gruber, U. F., Duchert, F., Fridrich, R., et al.: Prevention of postoperative thromboembolism by dextran 40, low doses of heparin, or xantinol nicotinate, Lancet 1:207, 1977.
- String, S. T., and Barcia, P. J.: Complications of small dose prophylactic heparinization, Am. J. Surg. 130:570, 1973.
- Pachter, H. L., and Riles, T. S.: Low dose heparin: Bleeding and wound complications in the surgical patient, Ann. Surg. 186:669, 1977.
- Gurewich, V., Nunn, T., Thazhathekudyil, T., et al.: Hemostatic effects of uniform low-dose subcutaneous heparin in surgical patients, Arch. Intern. Med. 138:41, 1978.
- Galle, P. C., Muss, H. B., McGrath, K. M., et al.: Thrombocytopenia in two patients treated with low-dose heparin, Obstet. Gynecol. 52:95, 1978.
- 6. Hrushesky, W.: Thrombocytopenia induced by low-dose subcutaneous heparin, Lancet 2:1286, 1977.

#### Reply to Dr. Clarke-Pearson

To the Editors:

In one of the early studies by Kakkar and associates,<sup>1</sup> it was shown that heparin levels were at their highest between 2 and 6 hours after subcutaneous injection of

472 Correspondence

5,000 U of heparin. However, during surgery the plasma heparin levels decrease much more rapidly than in normal individuals. Therefore, coagulation studies in our report were done not during or immediately after surgery but at 24 and 72 hours postoperatively in order to examine the maximum effect of heparin. The blood samples were drawn 3 to 5 hours after the previous heparin dose. The timing of the studies was carefully planned and tests were done at the optimum times to evaluate changes caused by heparin. They were not "improperly timed."

We are well aware of the problem of thrombocytopenia induced occasionally in patients by both therapeutic intravenous doses of heparin and low-dose subcutaneous heparin. However, in this study the heparin was continued for only 5 days postoperatively and the chances of heparin-induced thrombocytopenia were reduced as compared to use of high-dose heparin for longer periods of time following surgery.

As pointed out in our paper we saw none of the hyperresponsiveness to heparin as reported by Gurewich and colleagues.<sup>2</sup> In spite of increases of two times the control partial thromboplastin times in 10% to 15% of patients, only three (4.5%) of the patients of Gurewich and colleagues had excessive bleeding. One of these three had ingested aspirin.

The incidence of bleeding complications during heparin therapy reported by some authors is indeed bothersome. Other authors have seen no significant differences in bleeding between control subjects and patients receiving low-dose heparin. Kakkar and associates<sup>3</sup> in a multicenter study of 1,475 patients found no significant differences in number of patients requiring transfusion, in mean volume of blood transfused, or in mean drop of hematocrit between heparinized and control patients. Although our group of heparinized patients was only half as large as that of Pachter and Riles, 4 by their statistics we should have seen 7 or 8 patients with wound hematomas or hematuria. We had one patient with hematoma in the heparinized group and four patients with wound dehiscence or hematoma in the control group.

In the group studied in our report where extensive pelvic surgery was performed, many for malignancies (exenterations, radical vulvectomies, or radical hysterectomies with bilateral salpingo-oophorectomy and pelvic node dissection), the risk of pelvic vein thrombosis and pulmonary embolism is *high* (not low as Dr. Clarke-Pearson states). Therefore, such bleeding complications as wound hematoma or hematuria (which is seldom caused by heparin), as reported by Pachter and Riles, may be minor as compared to the danger of deep vein thrombosis and thromboembolism.

Our study of 75 patients showed that there were no significant changes caused by low-dose heparin in coagulation tests which would normally be used to monitor patients. The only exception to this is in the

levels of fibrin degradation products, which were much lower in the heparinized group. (There is an error in the abstract of our paper in line 5 which should have read, "There was a statistically significant decrease noted in fibrin degradation products...." The statements in the "Results" and "Comment" sections are correct.) This indicates that the amount of fibrin deposition is less in the heparinized patients which is a distinct advantage.

The bleeding seen in these elderly and often debilitated patients on subcutaneous low-dose heparin is much less than that in those given therapeutic doses of heparin starting 2 days after surgery with subsequent oral anticoagulation. Such anticoagulation has previously been routine treatment at this institution for radical pelvic surgery.

The criteria for "excessive clinical bleeding attributable to low-dose heparin" was observation by one or both of two experienced pelvic surgeons (Drs. Dillon and Chung), estimated blood loss during surgery, and incidence of postoperative anemia.

Louise Lang Phillips, Ph.D.

428 West 59th Street New York, New York 10019

#### REFERENCES

- Kakkar, V. V., Corrigan, T., Spindler, J., et al.: Efficacy of low doses of heparin in prevention of deep-vein thrombosis after major surgery, Lancet 2:101 1972.
- bosis after major surgery, Lancet 2:101 1972.
   Gurewich, V., Nunn, T., Thazhathekudyil, T., et al.: Hemostatic effects of uniform low-dose subcutaneous heparin in surgical patients, Arch. Intern. Med. 138:41, 1978.
- 3. Kakkar, V. V., Corrigan, T. P. Fossaid, D. P., et al.: Prevention of fatal postoperative pulmonary embolism by low doses of heparin, Lancet 2:45, 1975.
- 4. Pachter, H. L., and Riles, T. S.: Low dose heparin: Bleeding and wound complication in the surgical patient, Ann. Surg. 186:669, 1977.

#### Obstetric care of Southeast Asian refugees

To the Editors:

The Center for Disease Control has recently published a clinician's guide to diseases of Indochinese refugees. Although these guidelines cover many of the disease states encountered in these refugees, notably absent, however, is an acknowledgement that the pregnant Southeast Asian refugee may represent an important public health hazard both to her unborn child and to obstetric and neonatal care personnel.

Physicians and nurses involved in the obstetric care of Southeast Asian refugees should be alerted that these women may be acutely or chronically ill with such diseases as hepatitis B, tuberculosis, malaria, a variety of intestinal parasite infections, and a variety of hemoglobinopathies. Detection early in pregnancy of any such illness would seem advisable not only because obstetric management might be influenced by diag-

Volume 138 Number 4

noses such as chronic active hepatitis or a hemoglobinopathy but also so that, when infectious diseases are diagnosed, appropriate isolation precautions could be planned for the intrapartum hospitalization and, where indicated, arrangements for early prophylaxis of or surveillance for disease in the newborn infant could be made.

In specific terms, pregnant Southeast Asian refugees should be screened in early pregnancy with at least a hemoglobin electrophoresis, a hepatitis B surface antigen determination, a stool analysis for ova and parasites, and a tuberculin skin test. The many women who have a positive tuberculin skin test should be evaluated further for active tuberculosis and an effort should be made to ensure that no other family member has active tuberculosis. Additional unusual diseases, such as malaria, should be considered in women with suggestive symptoms.

Attention to these special concerns for the pregnant Southeast Asian refugee will, at the very least, improve the obstetric care of these women and may minimize the health risk which they can present both to their newborn infants and to the physicians and nurses involved in their care.

David F. Wender, M.D.

Department of Pediatrics Maine Medical Center Portland, Maine 04102

# Correlation between computed variability indexes and subjective evaluation

To the Editors:

In a recent article by Escarcena and associates, entitled "Fetal baseline heart rate variability estimation. I. Comparison of clinical and stochastic quantification techniques" (Am. J. Obstet. Gynecol. 135:615, 1979), the authors concluded that correlation between visual subjective and stochastic methods was low. According to the authors the study was started because there had been no attempt to correlate the computed variability indexes with the subjective evaluation of variability. They failed to cite a report¹ in this Journal in which similar conclusions were reported. This study also showed that the obstetric staff can be taught to evaluate the two components of variability with greater precision.

Veikko Kariniemi, M.D.

1st Department of Obstetrics and Gynecology Helsinki University Central Hospital Haartmanink. 2 00290 Helsinki 29, Finland

#### REFERENCE

1. Kariniemi, V.: Evaluation of fetal heart rate variability by a visual semiquantitative method and by a quantitative statistical method with the use of minicomputer, Am. J. Obstet. Gynecol. 130:588, 1978.

#### **Erratum**

In the June 15, 1980, issue of the JOURNAL, in the article by Donowitz and Wenzel, entitled "Endometritis following cesarean section," on page 468, in Table II, the number corresponding to *Hospital cost* and *Controls* should have been \$1,252.57.

# **BOOKS**

# Books received

- Ambulatory Obstetrics. A Clinical Guide. Ronald S. Gibbs and C. E. Gibbs. 197 pages. New York, 1979, John Wiley & Sons, Inc. \$9.95 (soft cover).
- Emotion and Reproduction. Fifth International Congress of Psychosomatic Obstetrics and Gynecology. Proceedings of the Serono Symposia. Volumes 20A and 20B. Edited by L. Carenza and L. Zichella. 1399 pages, illustrated. New York, 1979, Academic Press, Inc. \$62.00 for both volumes.
- Fetal and Maternal Medicine. Edited by E. J. Quilligan and Norman Kretchmer. 680 pages, illustrated. New York, 1980, John Wiley & Sons, Inc. \$40.00.
- Human Parturition. Edited by Marc J. N. C. Keirse, Anne B. M. Anderson, and Jack Bennebroek Gravenhorst. 275 pages, illustrated. Hingham, Massachusetts, 1979, Kluwer Boston, Inc. \$44.75.

- Infectious Diseases. Focus on Clinical Diagnosis. Edited by Haragopal Thadepalli. 848 pages, illustrated. Garden City, New York, 1980, Medical Examination Publishing Co., Inc. \$23.50 (soft cover).
- Mind and Cancer Prognosis. Edited by Basil A. Stoll. 203 pages. New York, 1980, John Wiley & Sons, Inc. \$27.00.
- Quick Reference to OB-GYN Procedures. 2nd Edition. Hugh R. K. Barber, David H. Fields, and Sherwin A. Kaufman. 347 pages. Philadelphia, 1979, J. B. Lippincott Company. \$14.75 (soft cover).

# DALLAS

Continued growth in the Kaiser/Prudential Health Plan membership has created opportunities for Board eligible/certified physicians in: Obstetrics/Gynecology, General Surgery, Internal Medicine, Cardiology, Family Practice, Allergy, Pediatrics. Members of the Permanente Medical Association of Texas (PMAT) provide comprehensive outpatient and inpatient care for Health Plan members. Incomes are competitive and there is a comprehensive fringe benefit package including an incentive income program after two years with the Medical Group.

This is a fine opportunity for qualified physicians to combine an active medical career free of administrative concerns with the pleasures of living in a prosperous city of the Southwest.

Send curriculum vitae to: Paul Lairson, M.D. The Permanente Medical Association of Texas 7777 Forest Lane - Suite 2444 Dallas, TX 75230

Physicians are cordially invited to attend "Update in Obstetrics and Gynecology: 1981", a continuing medical education course to be held at the Caribe Hilton Hotel, Puerto Rico, March 1-6, 1981. The course is sponsored by the Departments of Gynecology and Obstetrics, The University of Puerto Rico School of Medicine and The Johns Hopkins University School of Medicine.

The course is designed for obstetricians and gynecologists and provides a thorough review of current concepts regarding the management of a variety of oncologic, gynecologic, endocrinologic and obstetric disorders.

The course has been approved for 25 cognates, Formal Learning, by The American College of Obstetricians and Gynecologists. As an organization accredited for continuing medical education, The Johns Hopkins University School of Medicine certifies that this continuing medical education activity meets the criteria for 25 credit hours in Category I of the Physician's Recognition Award, AMA and the LCCME.

. For further information contact:

 Program Coordinator, Continuing Education Turner Auditorium Room 19 710 Rutland Avenue, Baltimore, Maryland (301) 955-3168.

# Flagyl (metronidazole) 250 mg

#### Warning

Metronidazole has been shown to be carcinogenic in mice and possibly carcinogenic in rats. (See Warnings.)
Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the Indications section

Indications: For the treatment of symptomatic trichomoniasis in females and males when the presence of the trichomonad has been confirmed by appropriate laboratory procedures (wet smears and/or cultures). Also for the treatment of asymptomatic females when the organism is associated with endocervicitis, cervicitis, or cervical erosion, *T. vaginalis* infection is a venereal disease and therefore, asymptomatic sexual partners of treated patients should be treated simultaneously if the organism is present. The decision to treat an asymptomatic male partner who has a negative culture. or one in whom no culture has been attempted, is an individual one. In any event, the consort should be treated with Flagyl in cases of reinfection. Flagyl is also indicated for acute intestinal amebiasis (amebic dysentery) and for amebic liver abscess.

Contraindications: Evidence or history of blood dyscrasia, active organic disease of the CNS, the first trimester of pregnancy and a hypersensitivity to metronidazole.

Warnings: Flagyl should not be used in the first trimester of pregnancy (see Contraindications). Use with discretion during the second and third trimesters of pregnancy and restrict to those pregnant patients not cured by topical measures. Flagyl (metronidazole) is secreted in the breast milk of nursing mothers It is not known whether this can be injurious to the newborn.

If used during lactation, an alternative method of feeding may

Tumorigenicity Studies in Rodents. Metronidazole has shown evidence of tumorigenic activity in a number of studies involving

chronic, oral administration in mice and rats.

Most prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all five reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). One of the mouse studies revealed increases in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant

In two long-term toxicity studies in the rat there was a statistically significant increase in the incidence of various neo-plasms, particularly mammary tumors, among female rats on metronidazole over that noted in the control groups

Two lifetime tumorigenicity studies in hamsters have been

reported to be negative.

Metronidazole has been reported to potentiate the anti-coagulant effect of coumarin and warfarin resulting in a pro-longation of prothrombin time. This possible drug interaction should be considered when Flagyl is prescribed for patients on this type of anticoagulant therapy.

Precautions: Mild leukopenia has been reported during Flagyl (metronidazole) use: total and differential leukocyte counts are recommended before and after treatment with the drug, especially if a second course is necessary. Flagyl may interfere with certain chemical analyses for SGOT. Avoid alcoholic beverages during Flagyl therapy because abdominal cramps, nausea, vomitting, headaches and flushing may occur. Discontinue Flagyl promptly if abnormal neurologic signs occur. Exacerbation of candidiasis may occur. In amebic liver abscess, aspirate pus during metronidazole therapy.

Adverse Reactions: Nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, abdominal cramping, constipation, a metallic, sharp and unpleasant taste, furry tongue, glossitis and stomatitis possibly associated with a sudden overgrowth of Candida, exacerbation of vaginal candidiasis, an occasional reversible moderate leukopenia, dizziness, vertigo, incoordination, ataxia, convulsive seizures, peripheral neuropathy, fleeting joint pains, confusion, irritability, depression, weakness, insomnia, mild erythematous eruptions, urticaria, flushing, nasal congestion, dryness of the mouth, vagina or vulva, pruritus, dysuria, cystitis, a sense of pelvic pressure, dyspareunia, fever, polyuria, incontinence, decrease of libido, proctitis, pyuria and darkened urine have occurred in patients receiving the drug. Patients receiving Flagyl may experience abdominal distress, nausea, vomiting, flushing or headache if alcoholic beverages are consumed. The taste of alcoholic beverages may also be modified. Flattening of the T-wave may be seen in ECG tracings.

Searle & Co. San Juan, Puerto Rico 00936

Address medical inquiries to: G. D. Searle & Co.
Medical Communications Department, Box 5110
Chicago, Illinois 60680



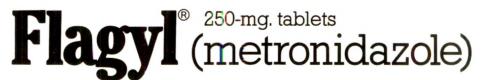
# His trichomoniasis can make her therapy useless unless they both take...

When the male is not treated for *Trichomonas vaginalis*, the female—no matter how well she cooperates with therapy—probably will become reinfected. To arrest this infection/reinfection cycle, both infected partners <u>must</u> be treated simultaneously.

The only systemic trichomonacide—In the female, trichomoniasis is a multiorgan disease. Trichomonads invade the vagina, and are often deeply entrenched in the endocervix, Skene's and Bartholin's glands, the urethra, and the bladder. The male genitourinary tract has seven possible sites of infection. Only the systemic action of Flagyl can eliminate sequestered trichomonads from these sites; topical treatments are ineffective.

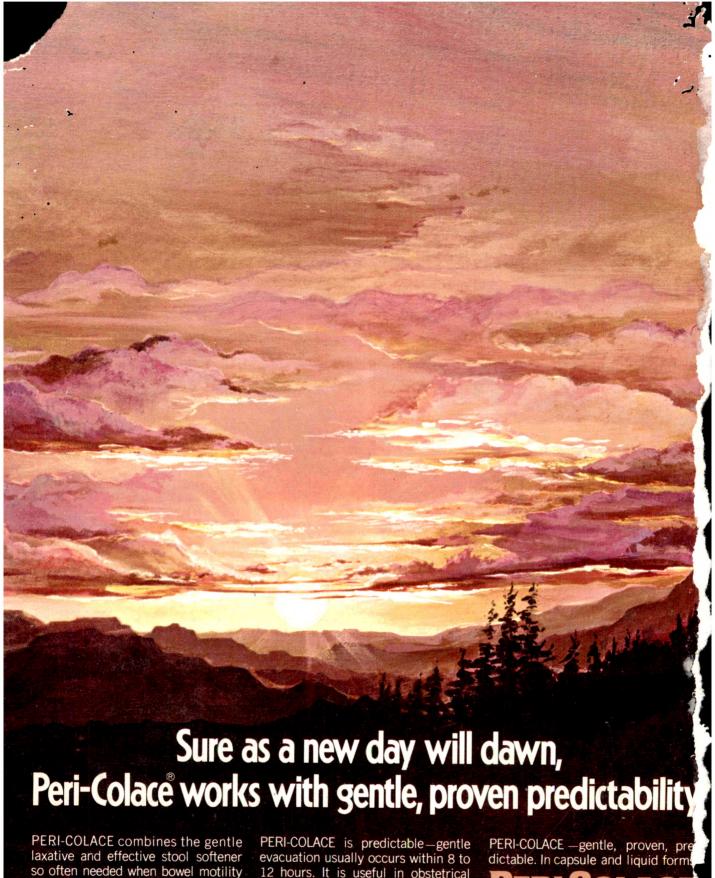
**Effective in both partners**—Because it reaches infection sites via the bloodstream, Flagyl is the only trichomonacide that is effective in both men and women. And Flagyl is the only available agent of its kind.

The only effective trichomonacide for couples



Please see adjacent page for brief summary of prescribing information.





PERI-COLACE combines the gentle laxative and effective stool softener so often needed when bowel motility is depressed. PERI-COLACE acts gently to induce peristalsis, while the stool-softening agent lets natural intestinal water permeate stools.

PERI-COLACE is predictable—gentle evacuation usually occurs within 8 to 12 hours. It is useful in obstetrical patients, as well as in geriatrics, preand postoperative patients, the convalescent, in patients with medication-related suppression of bowel motility and children.

# **PERICOLAGE**

casanthranol and dioctyl sodium sulfosuccina Gentle laxative plus stool soften

Mead binson